

James Madison University JMU Scholarly Commons

Masters Theses

The Graduate School

Spring 2011

Variation in the branching pattern of the four major caudal vessels emerging from the external carotid artery

Sara B. Heltzel
James Madison University

Follow this and additional works at: <https://commons.lib.jmu.edu/master201019>

 Part of the [Biology Commons](#)

Recommended Citation

Heltzel, Sara B., "Variation in the branching pattern of the four major caudal vessels emerging from the external carotid artery" (2011).
Masters Theses. 232.
<https://commons.lib.jmu.edu/master201019/232>

This Thesis is brought to you for free and open access by the The Graduate School at JMU Scholarly Commons. It has been accepted for inclusion in Masters Theses by an authorized administrator of JMU Scholarly Commons. For more information, please contact dc_admin@jmu.edu.

Variation in the Branching Pattern of the Four Major Caudal Vessels

Emerging from the External Carotid Artery

Sara B. Heltzel

A thesis submitted to the Graduate Faculty of

JAMES MADISON UNIVERSITY

In

Partial Fulfillment of the Requirements

for the degree of

Master of Science

Biology

May 2011

ACKNOWLEDGEMENTS

It is with immense gratitude that I acknowledge the support of my graduate advisor Dr. David Jaynes. Your encouragement, guidance and confidence in me from beginning to end truly made my graduate experience an invaluable one. I also consider it an honor to have worked with the members of my graduate committee; Dr. Roshna Wunderlich, Dr. Mark Gabriele, and Dr. Robert Lee. Thank you all for your time and dedication during my years at James Madison University. And lastly, thank you to those individuals who gave the ultimate gift to science by donating themselves to medical research. Your selfless contribution is truly appreciated and admired.

TABLE OF CONTENTS

List of Tables	v
List of Figures	vi
Abstract	vii
 Objective & Purpose	 1
 Introduction	 3
Arterial Anatomy of the Neck	3
Variation Within the Carotid Arterial System: Prior Research	5
Neck Trauma and the Carotid Arterial System	9
Surgical Exploration vs. Pre-Operative Screening	12
Population Differences in Vasculature	14
Arterial Formation and Variation	15
Hemodynamics and Blood Flow	16
 Predictions	 8
 Materials & Methods	 19
Specimens	19
Measurements	20
Common Carotid Artery Bifurcation	20
Arterial Branch Origin Distance from Common Carotid Artery Bifurcation	21
Arterial Branch Origin Location	21
Statistical Analysis	22

Results	24
Common Carotid Artery Bifurcation.....	24
Arterial Branch Origin Distance from Common Carotid Artery Bifurcation	25
Superior Thyroid Artery.....	25
Lingual Artery	25
Facial Artery.....	25
Occipital Artery.....	25
Arterial Branch Origin Location.....	28
Superior Thyroid Artery.....	28
Lingual and Facial Arteries	28
Occipital Artery.....	29
 Discussion.....	 37
Variation Between Sexes.....	37
Variation Between Neck Side.....	49
Clinical Implications	42
Variation Among Ethnic Populations.....	45
Future Approches	48
 Literature Cited	 49

LIST OF TABLES

Table 1. Branches of the external carotid artery	3
Table 2. Literature Review: Variation in external carotid artery branching pattern.....	8
Table 3. Common carotid bifurcation and arterial branch origin distances from common carotid artery bifurcation.....	26
Table 4. Comparison of arterial origin location between sexes and neck side	30
Table 5. Univariate analysis of variance	32

LIST OF FIGURES

Figure 1. Branches of the external carotid artery	3
Figure 2. Variation in external carotid artery branching pattern.....	6
Figure 3. Anatomical zones of the neck.....	10
Figure 4. Aortic arches in the human embryo.....	15
Figure 5. Locating the level of common carotid artery bifurcation	20
Figure 6. Comparison of means of measurements between sexes and neck side	27
Figure 7. Comparison of arterial origin location between sexes and neck side.....	31
Figure 8. Carotid arterial system.....	33
Figure 9. Examples of common trunk arterial origins	34
Figure 10. Occipital artery originating from the internal carotid artery	35
Figure 11. Tortuous internal carotid artery	36
Figure 12. Side differences in the origin of the carotid arterial system	41
Figure 13. Predicting the location of the common carotid bifurcation using bony anatomical landmarks	44
Figure 14. Global study populations	45
Figure 15. Ethnic comparison: STA and LA/FA origin locations	47

ABSTRACT

The branching pattern of vessels emerging from the external carotid artery (ECA) displays considerable variation. Knowledge of this variation is of particular interest to clinicians. There are few reports in the literature assessing these differences with regard to sex and sidedness (i.e., branching patterns of the right vs. left neck). The objective of this study was to assess the origin of the four primary caudal branches of the external carotid artery: the superior thyroid (STA), lingual (LA), facial (FA), and occipital (OA) arteries, in addition to the level of common carotid artery bifurcation (CB), with regard to sex, and side. Additionally, variation within this study population was considered in the context of global variation.

Seventy-nine cadavers (37 male, 42 female) were studied (71 right necks, 68 left necks). All carotid bifurcations were observed cranial to a midpoint located centrally between the mastoid process and the suprasternal notch. No significant difference was found for the mean distance of CB from the midpoint with regard to sex ($p = 0.70$) or side ($p = 0.75$). The STA on the right side emerged from the CB/ECA more frequently than it did from the common carotid artery (CCA) (67% and 31%, respectively); however, on the left side, the STA emerged more frequently from the CCA than from the CB/ECA (57% and 43%, respectively) ($p = 0.003$). The STA also exhibited a significantly longer distance from CB on the left than on the right ($p = 0.006$). The LA and FA arose individually more frequently than from a common trunk (79% and 21%, respectively). The OA emerged below the origin of the FA more frequently than at/above the FA (55% and 44%, respectively). With regard to sex, branching pattern variation was similar for

the vessels studied. No considerable variation was noted between this populations and other ethnic populations for STA or LA/FA origin locations.

Variation in ECA branching pattern is substantial with respect to side but not sex or ethnicity. This information may assist clinicians in preventing iatrogenic arterial injury by creating awareness of differential ECA branching pattern between neck sides, and may also allow for decreased incision lengths during surgical intervention to the carotid arterial system.

OBJECTIVE & PURPOSE

The external carotid artery exhibits a highly variable branching pattern, and prior research indicates that population groups and neck sides may exhibit differential frequencies of arterial variation (Natis et al., 2011; Sanjeev et al., 2010; Vázquez et al., 2009; Klosek & Rungruang, 2008; Ozgur et al., 2008; Lo et al., 2006; Hayashi et al., 2005; Zümre et al., 2005; Toni et al., 2004; LuČev et al., 2000; Shintani et al., 1999; Kitagawa, 1993). The carotid arterial system is extremely vulnerable in instances of traumatic neck injury and craniofacial surgical procedures (Mangla & Sclafani, 2008; Ramadan et al., 1995; McConnell et al., 1994). It is important to realize that in the event of traumatic events and neck injury, there may be little or no time to perform routine pre-operative diagnostics to assess arterial branching pattern. In the absence of knowledge regarding carotid arterial system branching variation, iatrogenic consequences may occur. Variation between population groups (e.g., sexes, side), lack of time in emergency situations, and overwhelmingly low success rates associated with angiography (Biffi et al., 1998; Menawat et al., 1992; Jurkovitch et al., 1985) point to the medical obligation to both recognize and utilize arterial variation rates (between populations and neck sides) in instances of traumatic injury to the carotid arterial system to reduce the potential for iatrogenic injury.

The objective of this research project is to assess variation in the four caudal branches of the external carotid artery. The purpose of the current study is to provide data on common carotid arterial variation between sex and neck side that health care professionals can utilize to anticipate variation in instances of traumatic injury to the carotid artery system when implementation of pre-surgical patient screening is not

feasible due to time constraints, high cost, or lack of overall effectiveness. This information would be used to reduce iatrogenic injury to neck vasculature during emergency surgical interventions, or any surgical procedure in which prior analysis of variable anatomy has not been assessed (Mangla & Sclafani, 2008). Making this information available to health care professionals prior to performing surgical procedures will hopefully decrease unintended surgical treatment. As a result, unintended surgical error should decline, and patient distress and cost should decrease.

Previous studies have been performed in different demographic areas, and have encompassed many different ethnicities; however, there is little, if any, information available that specifically assesses external carotid arterial branching pattern of inhabitants of the United States. Therefore, this project will consider variation within local populations in the context of global variation.

In order to provide more information regarding vascular patterning in the carotid arterial system, I assessed the level of common carotid artery bifurcation, the origin locations of the four primary caudal branches of the external carotid artery (the superior thyroid, lingual, facial, and occipital arteries), and the distance of these four external carotid artery branches from the common carotid artery bifurcation with regard to sex and neck side.

INTRODUCTION

Arterial Anatomy of the Neck

The carotid arterial system is the main arterial blood supply to the head and neck. The common carotid artery typically bifurcates to form the internal and external carotid arteries at roughly the level of the third or fourth cervical vertebra. The internal and external carotid arteries supply mostly intracranial and extracranial structures, respectively. While the internal carotid artery is said to exhibit no branching as it ascends into the cranium, the external carotid artery typically presents eight branches (six true branches, and two vessels formed by its bifurcation near the temporomandibular joint) (Figure 1). Each branch of the external carotid artery supplies a specific region of the neck and/or face (Table 1); however, anastomoses form frequently, occurring between both ipsilateral and contralateral arteries.

Figure 1. Branches of the external carotid artery. Sagittal view of the external carotid artery and branches using 3D contrast-enhanced MR angiography. S.Thy. = Superior Thyroid artery, Fac. = Facial artery, Ling. = Lingual artery, P.A. = Posterior Auricular artery, Occ. = Occipital artery, Max. = Maxillary artery, S.T. = Superficial Temporal artery (Lohan et al., 2007).

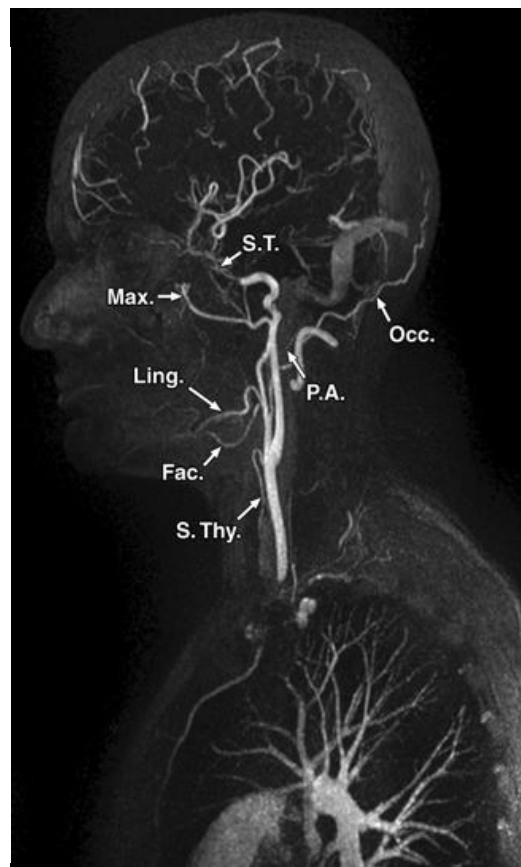


Table 1. Branches of the external carotid artery.

Branches of the External Carotid Artery (from caudal to cranial)	
*Superior Thyroid	Descends to supply the superior aspects of the thyroid gland and larynx, and the infrahyoid and sternocleidomastoid muscles
Ascending Pharyngeal	Supplies the pharynx, as well as the middle ear, cranial meninges, and prevertebral muscles
*Lingual	Courses anteriorly deep to the mylohyoid muscle and to provide the main blood supply to the tongue
*Facial	Courses superiorly over the border of the mandible to give off branches that supply the muscles and skin of the face, the area under the chin, and the palatine tonsils
*Occipital	Arises posteriorly and supplies the posterior scalp, as well as posterior neck and upper aspects of the back muscles
Posterior Auricular	Arises below the ear and supplies the auricle, parotid gland, facial nerve, and the posterior and lateral aspects of the scalp
Maxillary	One of the two terminal ECA branches; supplies the muscles of mastication, upper jaw (teeth), nasal cavities, maxillary sinus, and the dura mater surrounding the brain
Superficial Temporal	One of the two terminal ECA branches; supplies the frontal and temporal muscles, and the scalp covering the frontal and temporal regions

* Denotes ECA branches examined in this study

Variation Within the Carotid Arterial System: Prior Research

Blood vessel variation is prevalent within the human body, occurring in both the venous and arterial systems. Variations are categorized as normal or abnormal according to their frequency within the population and the associated degree of impact on health. Vessels exhibiting variation are typically those having an unusual origin or course that result from congenital abnormalities or pathologic conditions, or vessels that exhibit normal variation but occur in less than 50% of cases.

Previous studies have shown that multiple external carotid artery (ECA) branching patterns exist (Natis et al., 2011; Sanjeev et al, 2010; Vázquez et al., 2009; Klosek & Rungruang, 2008; Ozgur et al., 2008; Lo et al., 2006; Hayashi et al., 2005; Zümre et al., 2005; Toni et al., 2004; LuČev et al., 2000; Shintani et al., 1999; Kitagawa, 1993). The classic textbook representations of the ECA and the origin locations of its eight branches vary quite significantly depending on source (Moore et al., 2009; Gilroy et al., 2008; Drake et al., 2005; Netter, 2002). Variation in vessel origin and position has been noted most frequently for the superior thyroid, lingual, facial and occipital arteries (Figure 2 & Table 2).

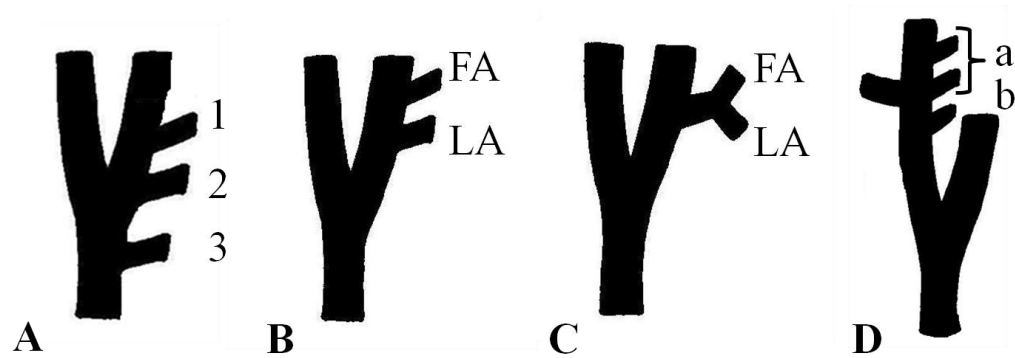


Figure 2. Variation in external carotid artery branching pattern. (A) Variation in the origin of the STA; STA origin **1)** from the ECA, **2)** from the level of the CB, and **3)** from the CCA. **(B)** and **(C)** Variation in the LA and FA origins; **(B)** LA and FA originating individually from the ECA. **(C)** LA and FA originating from a common lingual-facial trunk. **(D)** Variation in the origin of the OA; OA originating **a)** at/above the level of, and **b)** below the origin of the FA.

The superior thyroid artery (STA) is defined in most anatomical texts as being the first and most caudal branch of the ECA (Moore et al., 2009; Gilroy et al., 2008; Drake et al., 2005; Netter, 2002); however, reported STA origin location varies substantially between studies (Natis et al., 2011; Vázquez et al., 2009; Klosek & Rungruang, 2008; Ozgur et al., 2008; Lo et al., 2006; Hayashi et al., 2005; Zümre et al., 2005; Toni et al., 2004; Lučev et al., 2000; Shintani et al., 1999; Kitagawa, 1993). The STA is reported to originate most often from the external carotid artery or from the level of common carotid artery bifurcation (~ 75% of cases), and less often from the common carotid artery (~25%; a pattern rarely acknowledged in standard anatomical texts).

The lingual and facial arteries typically present as individual ECA branches superior to the origin of the STA. These arteries have also been described as originating from a common trunk (lingual-facial trunk). While individual origins are reported to occur most

often (~75-80% of cases), common lingual-facial trunks are frequently encountered (~20-25%), which is contrary to patterns demonstrated in anatomical texts.

The occipital artery is described as the most caudal posterior branch of the external carotid artery. It is classically depicted as originating most often in close proximity to the facial artery origin; however, the occipital artery is reported to have a variety of origin locations, ranging from at/above the facial artery origin to well below the origin of the lingual artery (Hayashi et al., 2005; Shintani et al., 1999).

Insufficient knowledge regarding the origin and course of blood vessels make surgical procedures potentially dangerous; thus, arteries exhibiting unusual patterns or infrequently encountered courses are very often the cause of iatrogenic injury (Malnar et al., 2010; Mangla & Sclafani, 2008; Chleboard & Dawson, 1990). The failure to adequately map vessels prior to surgical procedures can result in unintentional intraoperative vascular damage. Standard anatomical and surgical landmarks often become ineffective in deducing vessel identity, placement, and course. Additionally, while arterial variation goes unrecognized throughout an individual's life, pathological processes such as vascular disease and changes in vessel structure and elasticity can cause asymptomatic variation to become symptomatic, thus increasing their clinical importance (Gluncic, 2001).

Table 2. Literature review: variation in external carotid artery branching pattern. Summary of published articles relating to ECA branching pattern. Significant asymmetry in ECA branching pattern was commonly reported between neck sides; however, no significant variation in ECA branching pattern between the sexes was noted for any of these studies.

	Natsis et al., 2011*	Sanjeev et al., 2010	Vázquez et al., 2009*	Klosek et al., 2008*	Ozgur et al., 2008	Lo et al., 2006*
ECA Branch	N = 100 %	N = 74 %	N = 207 %	N = 72 %	N = 40 %	N = 67 %
STA						
ECA	39	65	24	33	25	46
CB	49	0	49	0	40	52
CCA	12	35	27	67	35	2
LA/FA						
Individual		78			89	76
Common Trunk		19			8	24
Other		3			3	0
OA						
At/Above FA						
Below FA						

	Hayashi et al., 2005	Zümre et al., 2005	Toni et al., 2004*	LuČev et al., 2000	Shintani et al., 1999*	Kitagawa, 1993*
ECA Branch	N = 98 %	N = 40 %	N = 4384 %	N = 40 %	N = 58 %	N = 74 %
STA						
ECA	70	25	64	30	100	54
CB	0	70	0	22	0	27
CCA	30	5	36	48	0	19
LA/FA						
Individual	81	80		80	69	
Common Trunk	18	20		20	31	
Other	1	0		0	0	
OA						
At/Above FA	57				100	
Below FA	43				0	

* Side differences were noted.

No significant sex differences were noted in the above studies.

Neck Trauma and the Carotid Arterial System

Neck trauma accounts for 5-10% of all serious traumatic injuries in the United States, resulting in approximately 3,500 deaths each year (Levy & Gruber, 2010). Studies have shown that the carotid arterial system (i.e., the common carotid artery, internal and external carotid arteries, and the branches of the external carotid artery) is the most commonly injured arterial structures in patients with traumatic neck injuries (McConnell et al., 1994). Iatrogenic consequences regarding the carotid system result most often from inadvertent damage to its branches during surgical procedures within the highly vascularized neck.

Neck injuries are classified according to their position relative to three distinct anatomical zones, and injury management is often based on injury location within these zones (Monson et al., 1969) (Figure 3). Zone I extends from the level of the clavicles and sternal notch (~T3 vertebral level) to the cricoid cartilage. Zone II, the largest and most vulnerable area of the neck, extends from the cricoid cartilage to the angle of the mandible. Zone III extends from the angle of the mandible to the skull base. Zone II is the most vulnerable neck zone due to the lack of bony protection for underlying soft tissue structures, and exhibits the highest incidences of penetrating neck trauma/injury. Data from a study by Bell et al. (2007) supports this; of 65 patients presenting neck injuries, 16% were located in zone I, 64% in zone II, and 20% in zone III.

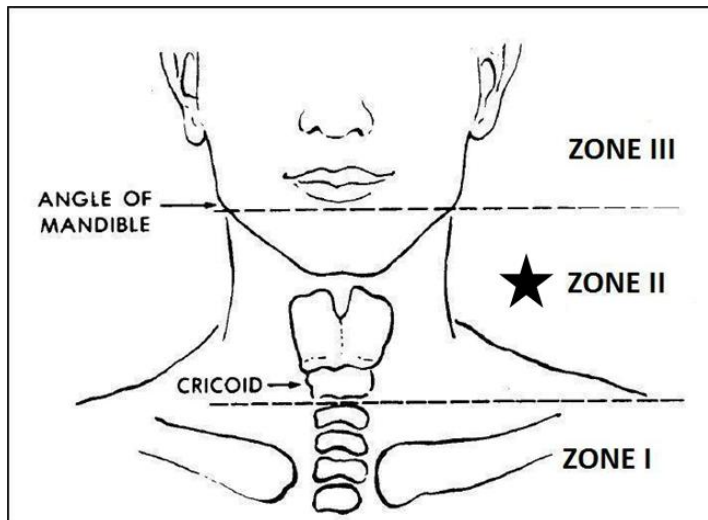


Figure 3. Anatomical zones of the neck. Zone II (★) is the most vulnerable to penetrating neck trauma, and exhibits the highest incidence of injury to the common carotid arterial system (Roon & Christensen, 1979).

The carotid arterial system (i.e., the common carotid artery, internal carotid artery, external carotid artery, and branches of the external carotid artery) is predominantly located in neck zone II. Injury to this system is recognized as a serious and potentially life-threatening condition. The common carotid artery was the most commonly injured arterial structure regarding neck trauma, with damage occurring in approximately 7% of patients (McConnell et al., 1994). Carotid vascular trauma exhibits high morbidity, accounting for a mortality rate of as high as 17% (Ramadan et al., 1995). Virtually all traumatic injuries to zone II of the neck require some form of surgical intervention to maintain patient stasis. Surgical intervention prompted by head and neck injury increases the potential for iatrogenic injury to the external carotid artery and its branches, potentially resulting in vascular damage that can exacerbate damage initially produced by the trauma (Mangla & Sclafani, 2008). A physician's knowledge of surrounding individual arterial variation may help prevent iatrogenic arterial injury.

Potential iatrogenic consequences include, but are not limited to, extreme blood loss (massive hemorrhage) as a result of arterial laceration/severance, thrombosis, pseudoaneurysm formation (also known as a "false" aneurysm; a dilation of an artery with actual disruption of one or more layers of the vascular wall), strokes and neurological complications, negative effects associated with prolonged hospital stay (risk of infection, cost, etc.) and surgical intervention (infection/anesthetics), and increased patient morbidity and mortality.

One of the most life-threatening effects of surgical injury to the carotid arterial system is massive hemorrhage and subsequent thrombosis. The carotid system is the main blood supply to the head and neck, supplying both intra- and extracranial structures. There is extensive collateral blood flow between the ipsilateral branches of the external carotid artery and other craniofacial arteries/contralateral external carotid artery which, in cases of severe hemorrhage, can lead to failed attempts to stop excessive bleeding. In trauma patients, massive hemorrhage and gross anatomical distortion may already be a factor. Thus, increased frequencies of iatrogenically-induced hemorrhage could potentially result in increased rates of patient mortality.

The external carotid artery and its branches lie more superficially than does the internal carotid artery. The superficial position of the external carotid artery, along with its variable branching pattern, results in an increased risk of injury. Intraoperative complications and incident rates regarding arterial injury are very rarely described in the literature; however, injury to the external carotid artery branches has been reported to occur most often during neck and craniofacial surgical procedures (Inamasu, 2005). Injuries to the external carotid arteries, though representing a small percentage of

iatrogenic vascular traumas, are notably difficult to diagnose and treat (Ditmars et al., 1997).

Iatrogenic damage to the external carotid artery results most often from inadvertent damage to its branches during surgical procedures within the neck. Emergency surgical intervention is often necessary in instances of neck trauma due to severe vascular and soft tissue injuries. External carotid artery injuries often present as a complex cause of exsanguinating hemorrhage (Mangla & Sclafani, 2008), and involvement of branches of the external carotid artery are more common than involvement of the external carotid artery itself (Nicoucar et al., 2008). Massive hemorrhage from carotid artery laceration makes surgical intervention immediately necessary to obtain hemodynamic stability. However, the probability of iatrogenic injury increases with the introduction of emergency surgical intervention.

Surgical Exploration vs. Pre-Operative Screening

The management of traumatic neck injuries is a controversial subject within the medical field. There is debate over whether immediate surgical exploration versus pre-operative imaging angiography results in superior patient treatment (Jarvik et al., 1995; Menawat et al., 1992; Hartling et al., 1989; Meyer et al., 1987). Angiography is a very common pre-operative imaging practice used to assess vascular anatomy. Angiography is a radiological visualization technique in which a radio-opaque dye is injected into blood vessels. The process typically takes one to two hours to complete, and can be prolonged if further investigation is deemed necessary by the radiologist.

Although commonly used, many authors suggest that angiography may not be the best choice in locating arterial injury or deducing arterial origin and course as compared to surgical examination, specifically in situations of traumatic injury to zone II of the neck. Angiography may even be completely unwarranted in certain instances (Jarvik et al., 1995; Menawat et al., 1992; Hartling et al., 1989; Meyer et al., 1987). A study conducted by Menawat et al. (1992) showed that angiography exhibited an extremely low yield (less than 0.1%) of findings significant enough to alter the plan of treatment in patients with zone II penetrating neck injuries. Jurkovitch et al. (1985) reported that only 9.4% of patients actually benefitted from diagnostic studies in which angiography located unrecognized vascular injury. In contrast, surgical examination exhibits relatively high success rates with regard to immediately locating and treating arterial injuries (Jurkovitch et al., 1985).

Additionally, routine angiography and other diagnostic tests can be extremely costly, time-consuming, and can overload available resources if used in all patients (Menawat et al., 1992). Jarvik et al. (1995) calculated the average cost of angiography as a screening tool to evaluate vascular injury in patients presenting zone II neck trauma to be over \$1500 per patient, accounting for 16% of the patient's total hospital costs. Many physicians feel it increasingly unnecessary to continue indiscriminate application of angiography due to the invasive nature of securing arterial access and high potential for technical imaging complications (Biffl et al., 1998).

Population Differences in Vasculature

The United States is rich in population diversity. The sex and ethnic population distribution of Virginia is similar to that of the United States as a whole. Both the United States and Virginia share a 49% male and 51% female sex population, and the United States population consists of 65% white, 12% black, 16% Hispanic, and 7% other (Virginia is 67% white, 19% black, 7% Hispanic, and 7% other) (U.S. Census Bureau, 2000). Previous studies have shown that multiple external carotid artery (ECA) branching patterns exist and that population groups (i.e., sexes, ethnicities) and neck sides may exhibit differential frequencies of arterial variation (Natis et al., 2011; Sanjeev et al., 2010; Vázquez et al., 2009; Klosek & Rungruang, 2008; Ozgur et al., 2008; Lo et al., 2006; Hayashi et al., 2005; Zümre et al., 2005; Toni et al., 2004; LuČev et al., 2000; Shintani et al., 1999; Kitagawa, 1993). Given the population distribution of the United States and Virginia, it is important to take into account that there may be correlations between populations and arterial variation frequencies, and that these frequencies may create differential health circumstances.

While anatomical variability regarding arterial characteristics (i.e., wall thickness, vessel diameter) between populations has been directly examined in other arterial systems (Lindekleiv et al., 2010; Eden et al., 2008; Schulz & Rothwell, 2001; Muller et al., 1991), little/no research has been done to directly evaluate the differences in ECA branching pattern and arterial origin and course specifically between populations, or between sides (i.e., right vs. left). By examining the effects of variable arterial origin and course within the ECA, it may be possible to better understand differential health and prevent the negative impacts associated with iatrogenic damage to these arteries.

Arterial Formation and Variation

The human embryonic cardiovascular system begins to form early in the third and fourth weeks of development and, like that of many other species, develops from a system of aortic arches (Liem et al., 2001; Gilbert, 2000) (Figure 4). The formation of the human embryonic cardiovascular system begins to occur early in development and is molded and differentiated over the first 12 weeks of development. Between developmental weeks 4-8, the six aortic arches undergo many morphological changes to form specific arterial derivatives. While the CCA, CB and ICA are derived from the third pair of aortic arches, the ECA and its branches are primarily derived from the first and second pair of aortic arches (Carlson, 2004; Moore & Persaud, 2003).

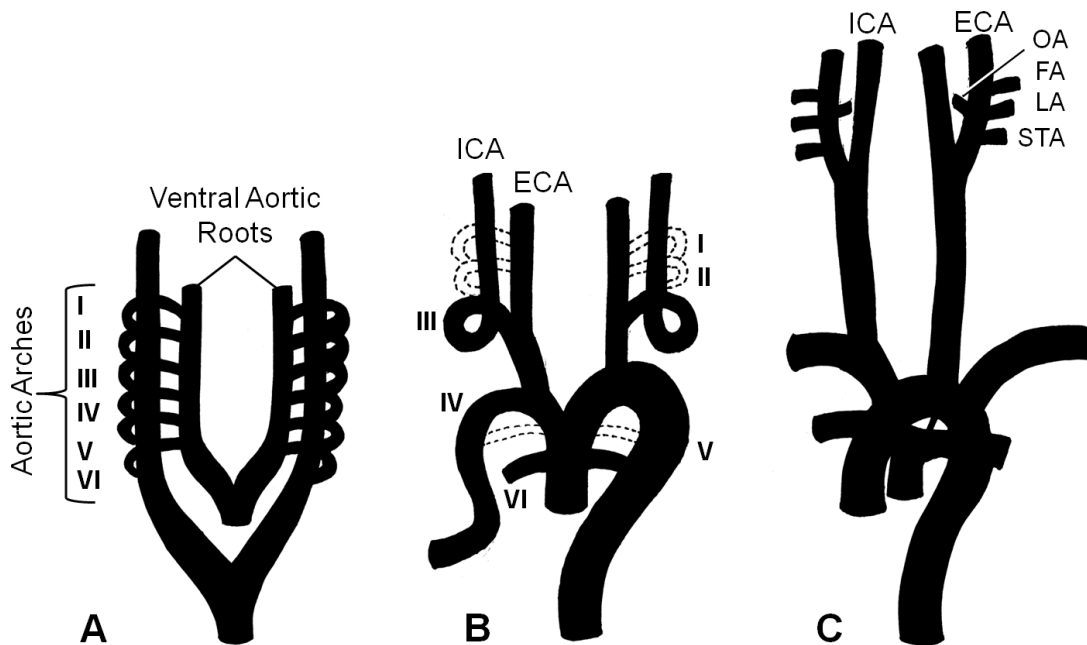


Figure 4. Aortic arches in the human embryo. (A) Schematic representation of the human embryonic aortic arch system at 4 weeks, at which point all six aortic arches are present. (B) The arches begin to undergo modification, and arches 1-2 disintegrate (indicated by the dotted lines). (C) Modification is completed to form the mature embryonic arterial system. (Adapted from Gilbert, 2000).

Variation in vessel structure may occur during the process of embryonic vessel formation and remodeling. The exact molecular mechanisms controlling arteriogenesis and driving vessel remodeling and vascular maturation remain unclear; however, variation in vessel origin and branching patterns have been attributed to an interaction between genetic and environmental (e.g., hemodynamics) cues. Through understanding the processes of embryonic vascularization, as well as the molecular and environmental cues driving these processes, it may be possible to better understand the cause of variation in vascular structures, to anticipate variation patterns, and to predict which structures might exhibit increased rates of variation.

Hemodynamics & Blood Flow

Remodeling of vessels via embryonic arteriogenesis is thought to be primarily hemodynamically cued. Vascular maturation is thought to be initiated by sudden hemodynamic changes that occur after the primary plexus of the cardiovascular system is connected to the embryonic aortic system (von Kodolitsch et al., 2004). The embryonic heart is formed at developmental day 20 and begins to beat early in the fourth week (days 21-22), pumping blood through the developing embryo and its primitive vasculature system. The introduction of circulatory blood flow causes the vessels to undergo remodeling (e.g., branching morphology, vessel diameter, etc.). The remodeling process thus forms a more mature hierarchical vascular pattern and results in arterialization of embryonic vasculature (Jones et al., 2006).

While an array of signals (molecular, hormonal, physical, etc.) are introduced to the developing embryo upon the introduction of blood flow, the simple force and pressure of

blood flow creates mechanical forces that effectively reshape the vessels and promote sprouting. Shear stress and resulting tangential forces promote vessel lengthening, while force perpendicular to the vessel creates circumferential stretch that widens the vessels (Jones et al., 2006). Mechanical pressures and stresses not only cause vascular morphological changes, but have also been shown to alter gene expression regarding vessel formation through activation of genetic pathways (Jones et al., 2004). Therefore, hemodynamics and differential protein expression are thought to act in conjunction to form and remodel embryonic vasculature (Jones et al., 2006).

The fetal circulatory system functions differently than that of the postnate (Figure 19). The fetus does not respire *in utero* due to its suspension in amniotic fluid. Therefore, the maternal body supplies the fetus with all oxygen needs via the placenta and umbilical cord. As a result, some fetal organs (e.g., lungs) are preferentially bypassed by the circulatory system. Three critical fetal shunts, the ductus venosus, foramen ovale, and ductus arteriosus, act in conjunction to facilitate right-to-left embryonic blood flow patterns that effectively bypass fetal pulmonary circulation.

The large right “side bias” of blood flow in the fetal cardiovascular circuit may have certain implications embryonic arteriogenesis, and subsequent vessel form and position. The increased blood flow to the right side of the fetus could create increased flow forces, or could introduce more growth factors (i.e., VEGF), which could spur differential bilateral vessel formation/remodeling between sides. Regarding ECA formation and variation, increased blood flow on the right side could potentially spur vessel growth and result in increased formation of common trunks prior to the formation of individual arterial branches.

PREDICTIONS

1) Variation Between Sexes

- Males will exhibit longer neck length (distance from mastoid process to suprasternal notch) than females due to sexual dimorphism.
- The level of CB and the CB to STA, LA, FA, and OA distances will not vary between the sexes.
- Branching pattern (i.e., STA, LA, FA, and OA origin locations) will not vary between the sexes.

2) Variation Between Neck Sides

- Neck length will not differ between right and left sides within an individual.
- The level of CB will be higher and the distance from CB to the STA, LA, FA, and OA origins will be longer on the right than on the left due to side asymmetry in the origin location of the carotid arterial system.
- Increased incidence of common origins (e.g., common lingual-facial trunks) will occur on the right side as compared with the left due to fetal blood flow patterning during the formation of embryonic vasculature.

3) Variation Between Ethnicities

- Arterial patterning within the carotid arterial system (specifically regarding the origins of the STA, LA and FA) will be similar among ethnic populations.

MATERIALS & METHODS

Specimens

Seventy-nine embalmed human cadavers (37 male; 42 female) from four Virginia universities (Eastern Virginia Medical School, Edward Via Virginia College of Osteopathic Medicine, James Madison University, and Virginia Commonwealth University) were studied to examine individual differences in external carotid arterial branching pattern variation with regard to sex and side. Both right and left necks were examined when available (71 right; 68 left). Digital images were taken of most specimens with a Nikon Coolpix S560 camera (Nikon, Japan). Dissection of the carotid arterial system was performed bilaterally on most cadavers. A few cadavers were previously prosected. The origin, course, and relations of each ECA branch were noted. Specimen ethnicity was determined from visual examination of specimens and from demographic information supplied by the State Anatomical Programs. The current study sample was predominantly Caucasian and exhibited very little ethnic variation (77 Caucasian, 1 African American, and 1 Asian American). All cadavers were acquired through the Virginia and West Virginia State Anatomical programs, thus this sample group represents individuals residing in the Eastern United States at time of death.

Measurements

Common Carotid Artery Bifurcation

The level of common carotid artery bifurcation (CB) was observed in relation to a midpoint located between the mastoid process and the suprasternal notch. The measurement technique used to identify the position of common carotid artery bifurcation is the same as that currently utilized clinically by vascular surgeons (Dr. Tara Balint, personal communication, November, 2010) (Figure 5).

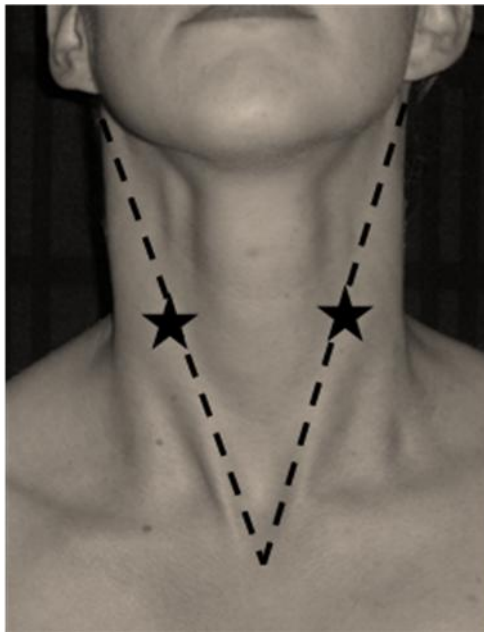


Figure 5. Locating the level of common carotid artery bifurcation. The length of an oblique line from the mastoid process of the skull to the suprasternal notch was measured bilaterally. The distance was averaged and halved to determine the midpoint (★) for each specimen. The level of common carotid bifurcation was measured cranially from the midpoint bilaterally.

Cadaver head/neck was aligned to as near anatomical position as possible, and an oblique line was generated from the mastoid process of the skull to the suprasternal notch, approximating the anterior border of the sternocleidomastoid muscle. The length of this line was measured in millimeters using electronic General No. 147 Digital Fractional Calipers (New York, USA) and was recorded bilaterally. An average neck length (mastoid process to suprasternal notch) was determined for each specimen in order

to account for any discrepancies in cadaver head positioning. The position of the CB was then recorded relative to the midpoint of this line on both right and left sides. The CB was utilized as the reference point for ECA branch measurements.

Arterial Branch Origin Distance from Common Carotid Artery Bifurcation

The distance between the superior aspect of the CB (i.e. the top of the bifurcation fork, at the location of the carotid body), and the origins of the STA, LA, FA and OA were measured in millimeter increments using electronic General No. 147 Digital Fractional Calipers (New York, USA). Measurements were taken from the superior aspect of the common carotid artery bifurcation to the middle of the arterial origin. If the lingual and facial arteries shared a common origin, the distance between the common carotid artery bifurcation and the origin of the common lingual-facial trunk was recorded.

Arterial Branch Origin Location

The level of common carotid artery bifurcation and the origin locations for the superior thyroid, lingual, facial, and occipital arteries were categorized as follows:

- The level of **common carotid artery bifurcation (CB)** in relation to a midpoint between the mastoid process of the skull and the suprasternal notch; bifurcating above, at the level of, or below the midpoint
- The origin of the **superior thyroid artery (STA)**; arising from the level of the carotid artery bifurcation/external carotid artery (CB/ECA), or from the common carotid artery (CCA)

- The origin of the **lingual (LA)** and **facial arteries (FA)**; individual origins, or arising from a common trunk
- The origin of the **occipital artery (OA)** in relation to the facial artery origin; at the level of/above the facial artery origin, or below the facial artery origin

In order to determine if an artery was “at the level of” another (e.g., the occipital artery origin location in relation to the facial artery; at/above the level of, or below the facial artery origin) the diameter midpoint of the artery being measured had to overlap the origin of the reference artery. When a common lingual-facial trunk was present, the artery being assessed was categorized according to the level of the trunk, as the trunk was accepted as the “origin” of the reference artery (i.e., the facial artery).

Statistical Analysis

All statistical analyses of arterial variation based on sex and side were performed using PASW version 18.0 statistical analysis software. Means, standard deviations, and ranges were determined for all measurements for the entire sample, as well as for each sex and side. Statistical analyses were performed in order to determine:

- *Between individual arterial variation* (for differences in variation frequency between the sexes)
- *Within individual arterial variation* (for differences in variation frequency between right and left sides of the neck)

Differences between the continuous research variables (i.e., the level of common carotid artery bifurcation, and the distances between the common carotid bifurcation and the superior thyroid, lingual, facial, and occipital arteries) were determined by conducting repeated measures ANOVA analyses, in which arterial origin distance from the common carotid artery bifurcation was the response variable, and sex and side were the two fixed factors. The repeated measures ANOVA allowed for the independence of one factor (sex) and the dependence of the other (side). Since no sex/side interaction was found for any of the distances, data could be combined and compared separately based on sex and side (Table 5). Differences were considered statistically significant at $p < 0.05$.

Differences between the categorical variables (i.e., the origin location for the superior thyroid, lingual, facial, and occipital arteries) were determined by conducting Fisher exact tests (Kirkman, 1996). Differences were considered statistically significant at $p < 0.05$. Regression analyses were performed to determine if relationships existed between the anatomical landmarks utilized in this study (i.e., neck length (distance from mastoid process to suprasternal notch) and midpoint) and the level of CB or the origin locations for the STA, LA, FA and OA.

RESULTS

Common Carotid Artery Bifurcation

The mean distance from mastoid process to suprasternal notch was 171.97 mm (Table 3). The mean midpoint value (measured cranially from the suprasternal notch) was 85.99 mm (Table 4). All common carotid bifurcations (CB) were observed cranial to the midpoint, with a mean distance (CB from the midpoint) of 24.66 mm cranially (Table 3). Males exhibited a significantly longer mastoid process to suprasternal notch distance than females ($p = 0.001$), and a significantly higher midpoint than females ($p < 0.005$) (Table 3, Figure 6A); the midpoint for males was approximately 8% higher than that for females. Side differences were also noted for the distance from mastoid process to suprasternal notch; the left neck was significantly longer than the right ($p = 0.04$). There was no significant difference for the midpoints between right and left sides ($p = 0.90$) (Table 3, Figure 6B). No significant difference was found for the mean distance of common carotid bifurcation from the midpoint with regard to sex ($p = 0.70$) or side ($p = 0.75$) (Table 3, Figure 6A & B).

Arterial Branch Origin Distance from Common Carotid Artery Bifurcation

Superior Thyroid Artery

The mean distance of STA origin from the CB was 3.87 mm. No significant difference was noted for the CB to STA origin distance between sexes ($p = 0.33$).

The left neck exhibited a significantly larger distance from the CB to STA ($p = 0.006$) (Table 3, Figure 6A & B).

Lingual Artery

The mean distance of LA origin from the CB was 12.21 mm. No significant difference was noted for the CB to LA origin distance between sexes ($p = 0.79$).

There was no significant difference in distances from CB to LA origin between right and left sides ($p = 0.94$) (Table 3, Figure 6A & B).

Facial Artery

The mean distance of FA origin from the CB to was 17.64 mm. No significant difference was noted for the CB to FA distance between sexes ($p = 0.97$). There was no significant difference in distances from CB to FA origin between right and left sides (Table 3, Figure 6A & B).

Occipital Artery

The mean distance of OA origin from the CB was 16.68 mm. No significant difference was noted for the CB to OA origin distance between sexes ($p = 0.45$).

There was no significant difference in distance from CB to OA origin between right and left sides ($p = 0.25$) (Table 3, Figure 6A & B).

Table 3. Common carotid artery bifurcation and arterial branch origin distances from common carotid artery bifurcation.

Measurements were recorded in millimeters.

	MP to Sup.Notch		MdPt		MdPt to CB	
	Mean +/- SD	p	Mean +/- SD	p	Mean +/- SD	p
Total (n = 112-114)	171.97 +/- 16.05		85.99 +/- 7.96		24.66 +/- 8.50	
Males (n = 25-27)	179.62 +/- 16.63	0.001*	89.81 +/- 8.20	< 0.005*	24.12 +/- 7.92	0.704
Females (n = 25-28)	165.46 +/- 12.50		82.73 +/- 6.22		24.94 +/- 9.06	
Right (n = 58-59)	171.95 +/- 16.10	0.044*	86.02 +/- 7.99	0.900	24.40 +/- 9.06	0.754
Left (n = 54-55)	173.13 +/- 16.12		85.95 +/- 8.00		24.66 +/- 7.94	
Male/Right (n = 27)	178.81 +/- 17.22		89.41 +/- 8.23		24.67 +/- 7.78	
Male/Left (n = 26)	179.85 +/- 16.31		89.92 +/- 8.34		24.00 +/- 8.20	
Female/Right (n = 31-32)	165.38 +/- 12.30		82.69 +/- 6.31		25.13 +/- 10.17	
Female/Left (n = 28-29)	165.83 +/- 12.94		82.91 +/- 6.23		24.75 +/- 7.82	

	STA		LA		FA		OA	
	Mean +/- SD	p	Mean +/- SD	p	Mean +/- SD	p	Mean +/- SD	p
Total (n = 124-126)	3.87 +/- 3.77		12.21 +/- 6.49		17.64 +/- 8.21		16.68 +/- 8.80	
Males (n = 25-27)	4.09 +/- 4.18	0.325	12.73 +/- 6.61	0.793	18.09 +/- 8.59	0.974	17.28 +/- 9.49	0.449
Females (n = 25-28)	3.40 +/- 3.33		12.28 +/- 6.42		18.16 +/- 7.87		15.65 +/- 8.18	
Right (n = 58-59)	2.77 +/- 2.63	0.006*	12.53 +/- 6.46	0.942	18.57 +/- 7.57	0.417	17.13 +/- 8.79	0.252
Left (n = 54-55)	4.73 +/- 4.37		12.47 +/- 6.56		17.68 +/- 8.86		15.80 +/- 8.79	

* Statistically significant ($p < 0.05$)

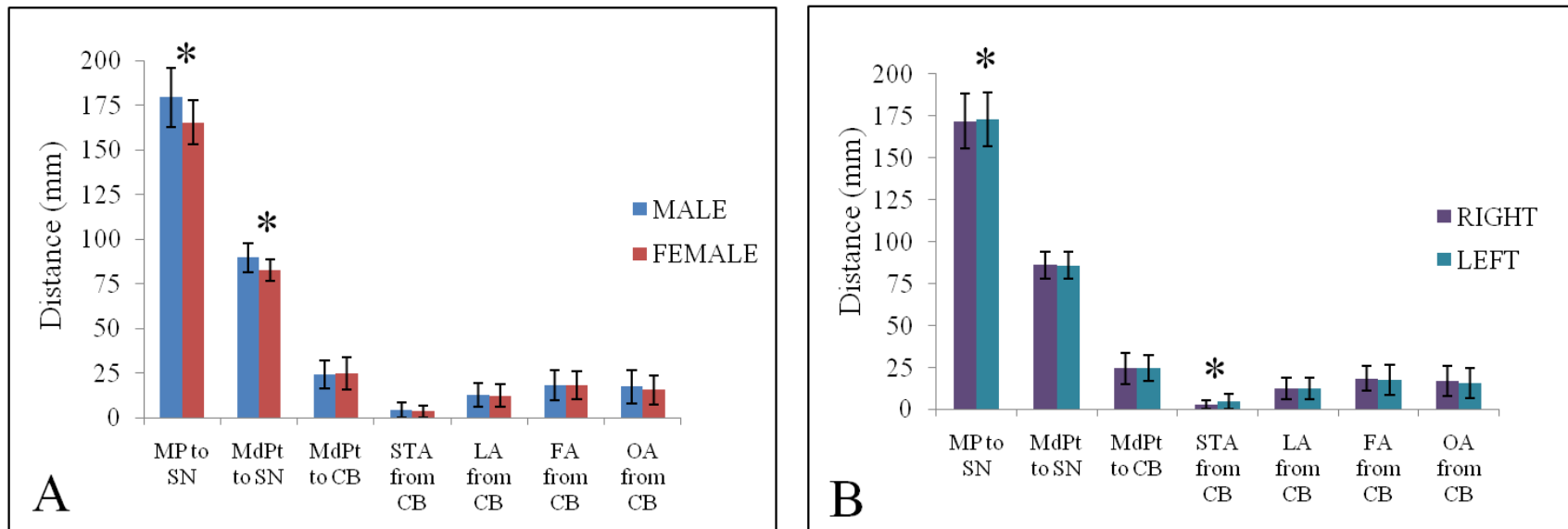


Figure 6. Comparison of means of measurements between sexes and neck side. (A) Males exhibited a significantly longer mastoid process to suprasternal notch distance (~ 8% longer) and a significantly higher midpoint (~ 8% higher) than females. (B) Significant differences between right and left side were noted for the midpoint to suprasternal notch distance, and the CB to STA distance. * $p < 0.05$. Error bars depict one standard deviation.

Arterial Branch Origin Location

Superior Thyroid Artery

The STA originated from the CB/ECA most often (55%) (Figure 8), although a large percentage (44%) did emerge from the CCA. Regarding side, results showed that the STA on the right side emerged from the CB/ECA more frequently than it did from the CCA; 67% (47/70) and 31% (22/70), respectively. However, on the left side, the STA emerged more frequently from the CCA than the CB/ECA; 57% (39/68) and 43% (29/68), respectively ($p = 0.003$). No significant differences in STA origin location were observed with regard to sex ($p = 0.67$) (Table 4, Figure 7A & E).

Lingual and Facial Arteries

The LA and FA arose individually from the ECA most frequently (79%); however, common trunks were commonly encountered (21%) (Figure 9A & B). No significant differences in origin location were observed with regard to sex or side for the LA ($p = 0.70$, $p = 0.38$, respectively) or for the FA ($p = 0.83$, $p = 0.21$, respectively) (Table 4, Figure 7C,D, G, H). Three specimens (2% of cases) displayed thyrolingual trunks, in which the LA and the STA shared a common origin (Figure 9C & D). One of the thyrolingual trunks originated from the ECA, one from the CB, and one from the CCA. While a thyrolingual trunk originating from the external carotid artery has an incidence rate of approximately 2.5% (Ozgur et al., 2008), a thyrolingual trunk originating from the common carotid

artery has been reported to occur in less than 0.1% of specimens (Lippert & Pabst, 1985).

Occipital Artery

The OA emerged below the origin of the FA more frequently than from at/ above (55% and 44%, respectively). No significant differences in origin location were observed with regard to sex or side for the OA ($p = 0.65$, $p = 0.42$, respectively) (Table 4, Figure 7B & F). One specimen displayed a rare branching pattern in which the occipital artery originated from the ICA (Figure 10). In cases of branching pattern variation involving the internal carotid artery, the occipital artery is the most common ECA branch to originate from the cervical segment of the internal carotid artery (Aggarwal et al., 2006).

Table 4. Comparison of arterial origin location between sexes and neck side. No significant difference in origin location was observed with regard to sex for the STA, LA, FA or OA. Significant difference was found for the STA origin location with regard to side. The STA on the right side emerged from the CB/ECA more frequently than it did from the CCA; however, on the left side, the STA emerged more frequently from the CCA than from CB/ECA. No significant difference in origin location with regard to side for the LA, FA or OA.

	TOTAL		MALE		FEMALE		p	RIGHT		LEFT		p
STA	(n = 138)		(n = 66)		(n = 72)		0.67	(n = 70)		(n = 68)		0.003*
	n	%	n	%	n	%		n	%	n	%	
CB/ECA	76	55	35	53	41	57		47	67	29	43	
CCA	61	44	31	47	30	42		22	31	39	57	
Other	1	1	0	0	1	1		1	1	0	0	
LA	(n = 139)		(n = 66)		(n = 73)		0.70	(n = 71)		(n = 68)		0.38
	n	%	n	%	n	%		n	%	n	%	
Individual	107	77	49	74	58	79		51	72	56	82	
Common Trunk	29	21	15	23	14	19		18	25	11	16	
Other	3	2	2	3	1	1		2	3	1	1	
FA	(n = 136)		(n = 66)		(n = 70)		0.83	(n = 69)		(n = 67)		0.21
	n	%	n	%	n	%		n	%	n	%	
Individual	107	79	51	77	56	80		51	74	56	84	
Common Trunk	29	21	15	23	14	20		18	26	11	16	
OA	(n = 124)		(n = 61)		(n = 63)		0.65	(n = 64)		(n = 60)		0.42
	n	%	n	%	n	%		n	%	n	%	
At/Above FA	55	44	28	46	27	43		31	48	24	40	
Below FA	68	55	32	52	36	57		33	52	35	58	
Other	1	1	1	2	0	0		0	0	1	2	

*Statistically significant ($p < 0.05$)

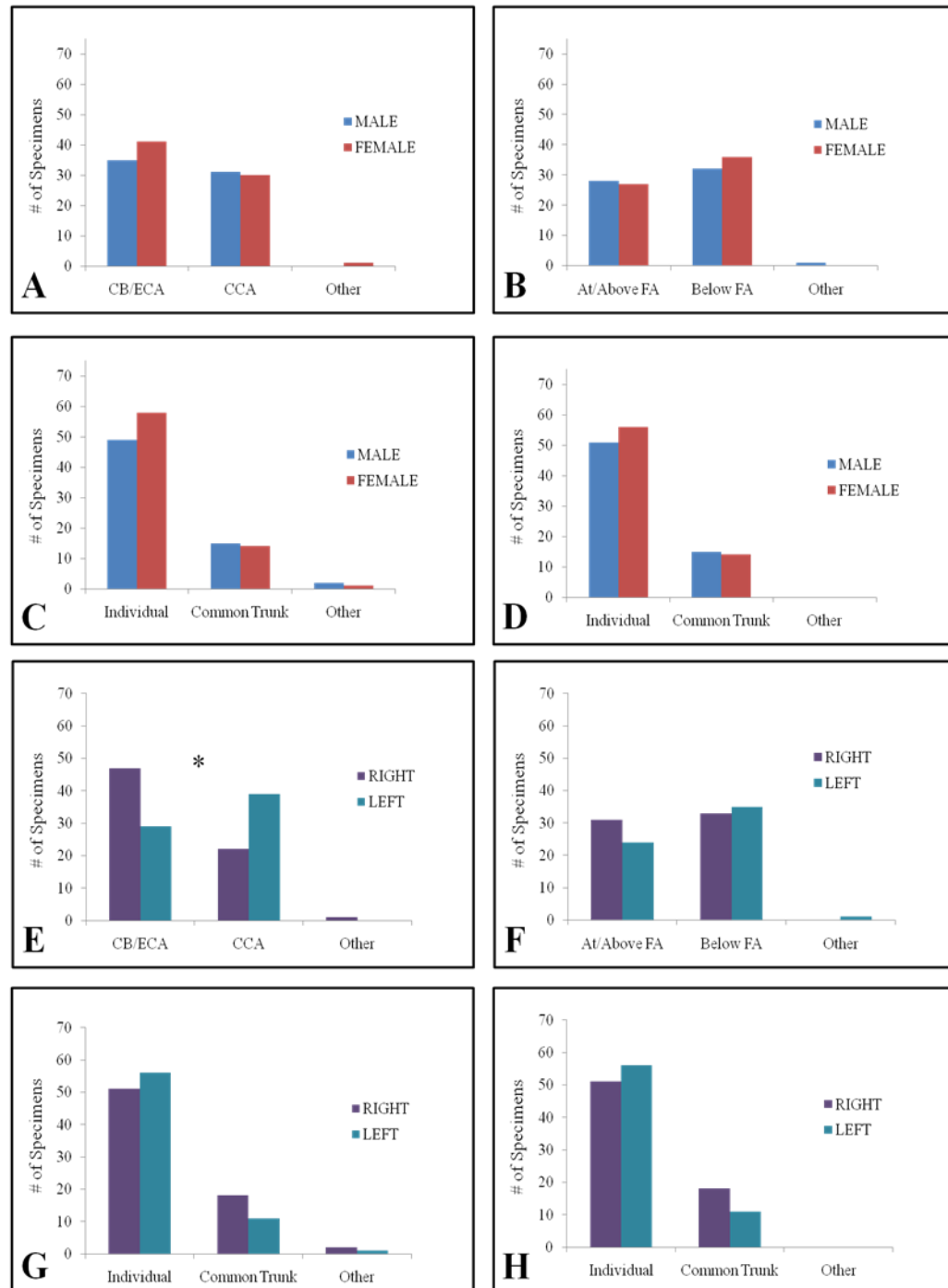


Figure 7. Comparison of arterial origin location between sexes and neck side.

(A & E) STA Origin Location, (B & F) OA Origin Location, (C & G) LA Origin Location, and (F & H) FA Origin Location. No significant difference in origin location was observed with regard to sex for the STA, LA, FA or OA. Significant side difference was found only for the STA origin location; the STA on the right side emerged from the CB/ECA more frequently than it did from the CCA; however, on the left side, the STA emerged more frequently from the CCA than from the CB/ECA.

Table 5. Univariate analysis of variance. Results of a repeated measures ANOVA assessing between and within subject effects. Significant sex differences were observed when comparing the distance from mastoid process to suprasternal notch and midpoint level. Significant side differences were observed when comparing the distance from mastoid process to suprasternal notch and the STA from CB distance. No sex/side interaction was found for any of the distances. MP = Midpoint, Sup.Notch = Suprasternal Notch, CB = Common Carotid Bifurcation, STA = Superior Thyroid Artery, LA = Lingual Artery, FA = Facial Artery, OA = Occipital Artery.

Response Variable	p		
	Sex	Side	Sex/Side Interaction
Distance			
MP to Sup.Notch	0.001*	0.044*	0.420
Midpoint	<0.005*	0.900	0.960
Midpoint to CB	0.704	0.754	0.986
STA from CB	0.325	0.006*	0.740
LA from CB	0.793	0.942	0.774
FA from CB	0.974	0.417	0.612
OA from CB	0.449	0.252	0.678

* Statistically significant ($p < 0.05$)

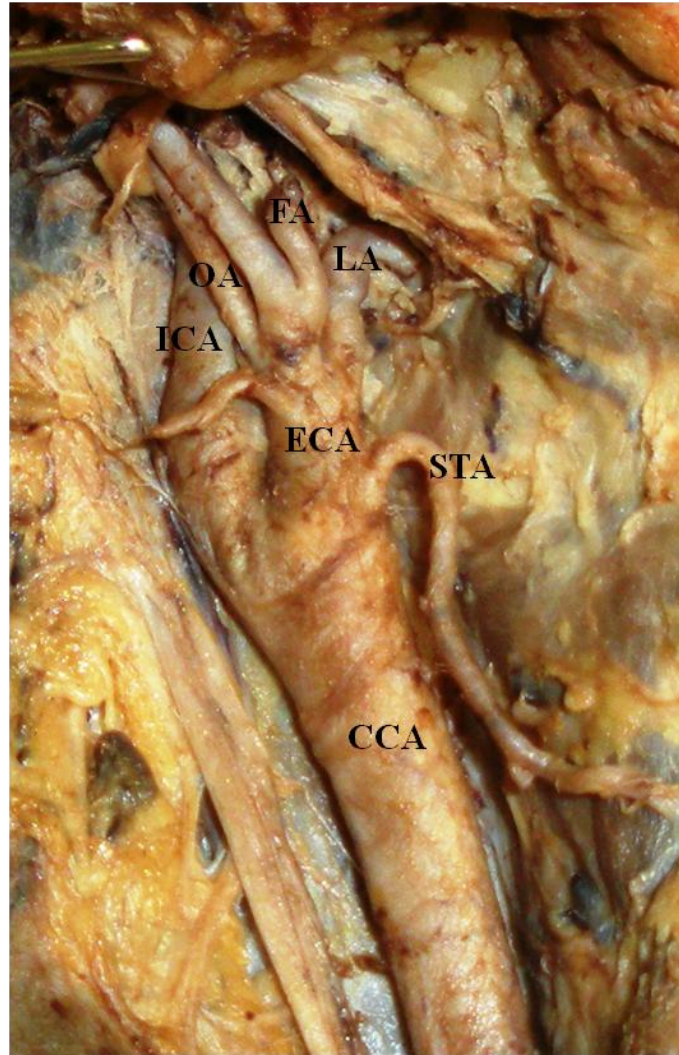


Figure 8. Carotid arterial system. Female; Right neck. This image is representative of the most common arrangement of ECA branching pattern noted in this study. The STA originates from the CB, the LA and FA exhibit individual origins, and the OA originates below the level of the FA origin.

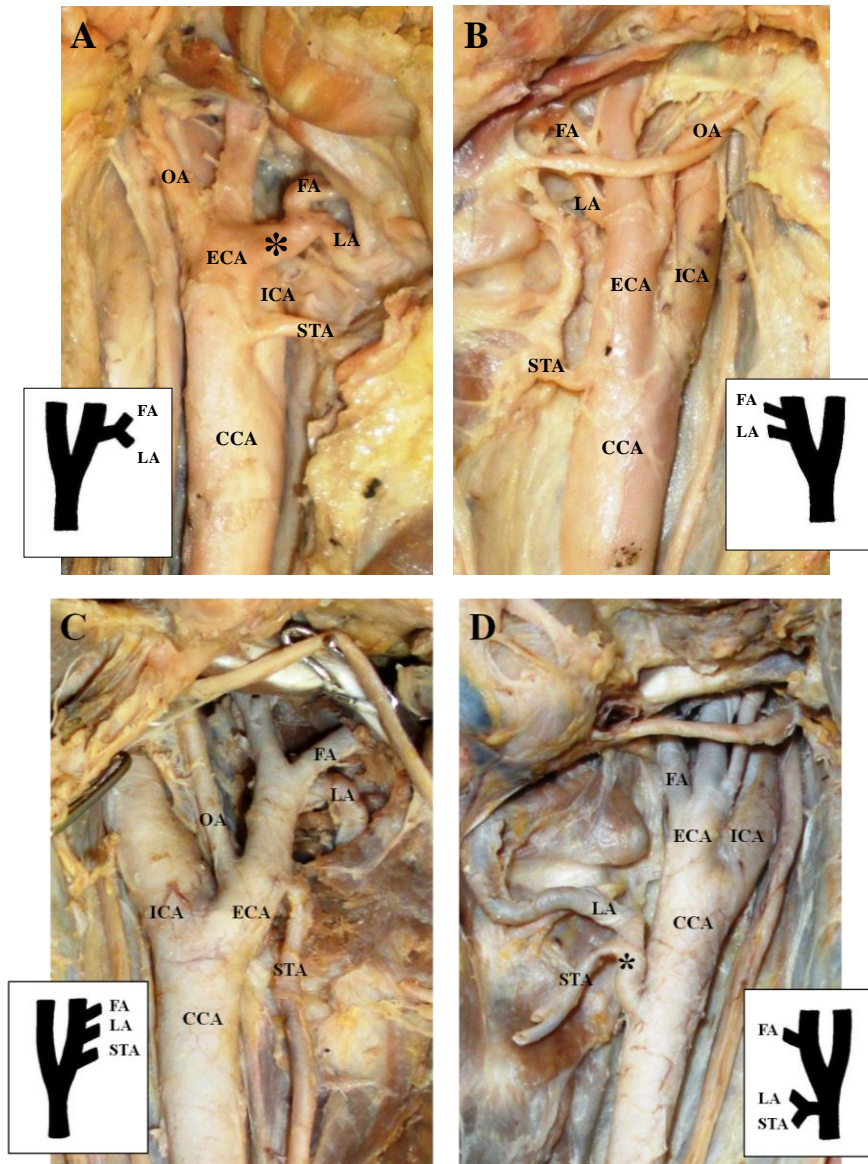


Figure 9. Examples of common trunk arterial origins. (A) & (B); insets are schematic drawings showing common LA and FA branching patterns. (A) Female, right neck; common LA/FA trunk, STA from CB. (*) denotes LA/FA trunk. (B) Female, left neck; individual LA and FA origins from the ECA, STA from the CCA. (A) and (B) are from the same female specimen. (C) & (D) insets are schematic drawings showing common STA, LA, and FA branching patterns. (C) Male, right neck; STA from the ECA, LA and FA from individual origins. (D) Male, left neck; the STA and LA originate from a common thyrolingual trunk branching from the CCA. (*) denotes the thyrolingual trunk. (C) and (D) are from the same male specimen.

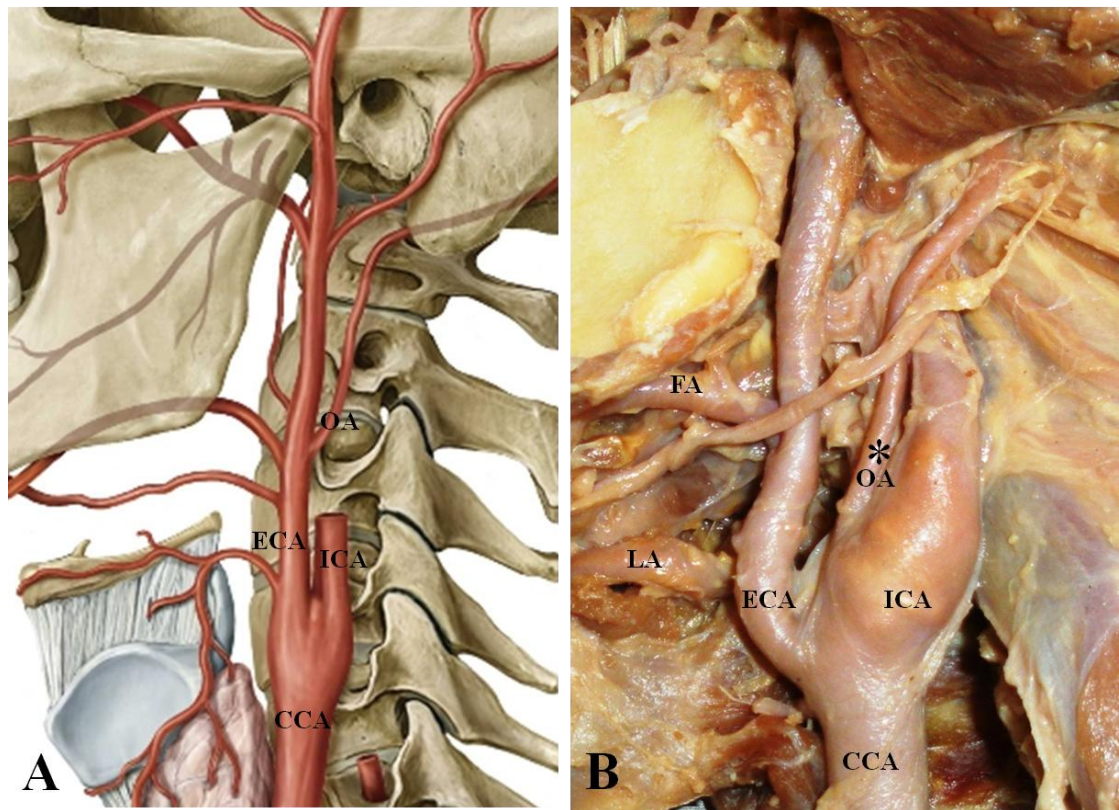


Figure 10. Occipital artery originating from the internal carotid artery.

(A) Anatomical textbook image showing the internal carotid artery demonstrating no branching as it ascends to the cranium (Gilroy et al., 2008). (B) Male, left neck; the OA, usually the most caudal posterior branch of the ECA, is shown originating from the ICA. (*) denotes the OA originating from the ICA. This additional bifurcation (between the aberrant OA and ICA) may have clinical implications for increased plaque build-up, which could potentially increase risk of stroke if a plaque embolus were to dislodge and travel up the ICA to the brain

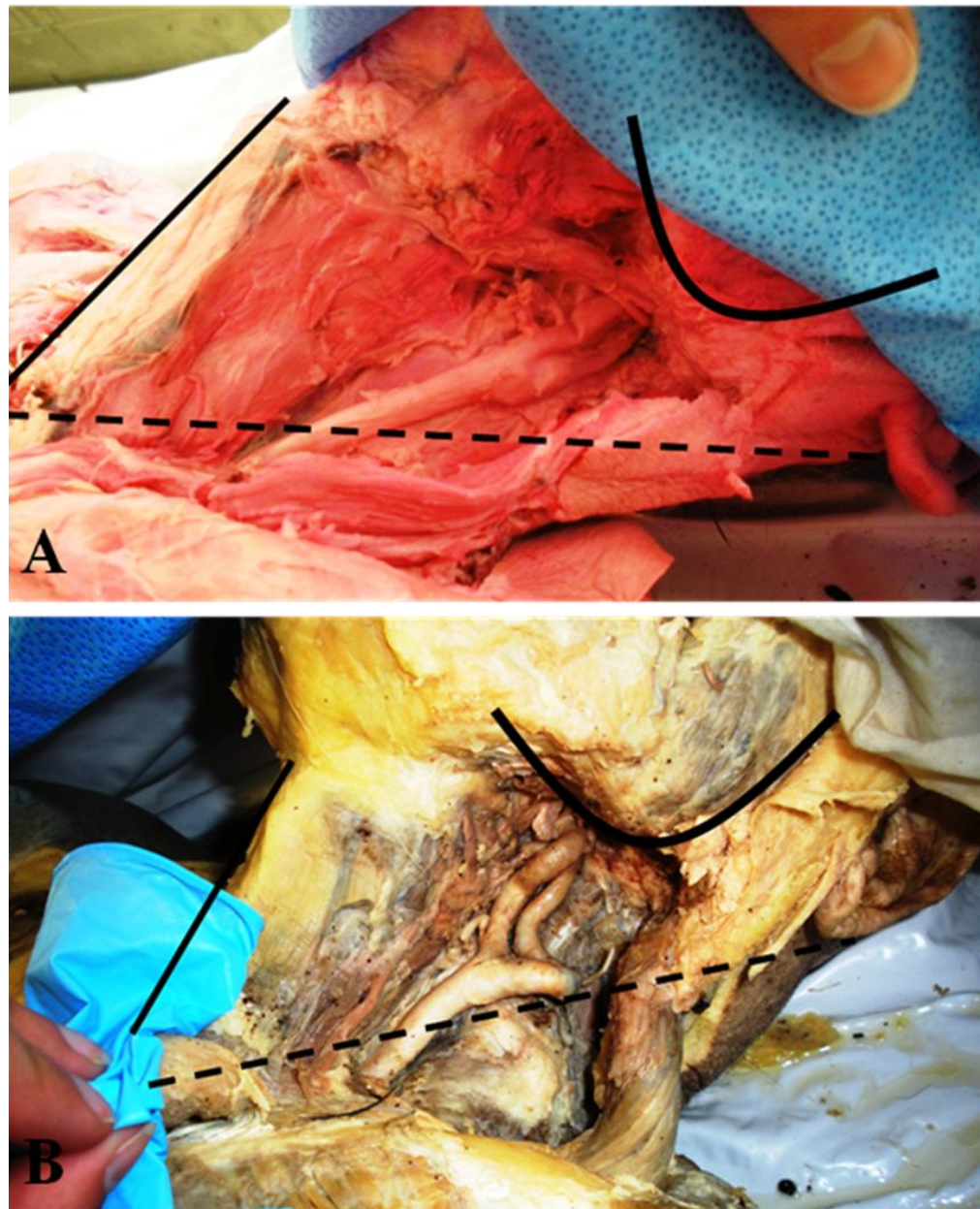


Figure 11. Tortuous internal carotid artery. (A) Male, left neck; this specimen exhibited a “textbook” common carotid arterial system, with straight internal and external carotid arteries. (B) Male, left neck; this specimen exhibited an extremely tortuous internal carotid artery. Large quantities of arterial plaque could be palpated at the angle of the tortuous ICA. Curved lines indicate the angle of the mandible; dotted lines represent an oblique line from mastoid process to suprasternal notch; solid lines indicate a midline from suprasternal notch to superior aspect of thyroid cartilage.

DISCUSSION

In summary, it was found that the STA origin location and distance from CB varied significantly between sides (but not between sexes), the LA and FA originated more frequently from individual origins than from a common trunk, and the OA originated more frequently from below the origin of the FA than from at/above the FA origin. No significant difference was found for the origin locations or distance from CB for the LA, FA or OA with regard side or sex. Therefore, we conclude that variation in the ECA branching pattern is substantial regarding side, but not so regarding sex. Further, our findings show that the origin of the STA from the CCA on the left side and the caudal origin of the OA differ significantly with the vast majority of ECA depictions shown in human anatomy atlases. This information may assist clinicians in anticipating arterial arrangements in situations where screening is impossible. Recognition and utilization of vascular variation rates regarding the branching pattern of the ECA between sexes and neck side may reduce the potential for iatrogenic arterial injury.

Variation Between Sexes

Results showed that males exhibited a significantly longer mastoid process to suprasternal notch distance than females (male neck length was ~8% longer), as well as a significantly higher midpoint (male midpoint was ~8% higher) ($p = 0.001$ and <0.005 , respectively). The significant difference in neck length between males and females can be attributed to sexual dimorphism; males are typically larger in size/taller than females, and would therefore exhibit longer neck lengths and higher midpoints. The average American male is approximately 8% taller than the average American female (Ogden et al., 2004).

Despite the 8% difference in neck length and midpoint between males and females, no significant difference was observed for the mean distance of common carotid bifurcation from the midpoint between sexes. Females actually exhibited a ~3% higher level of carotid artery bifurcation than did males relative to the length between mastoid process to suprasternal notch and midpoint.

This information may have clinical implications for locating the level of common carotid bifurcation and the length of incision made during surgical interventions to the carotid arterial system (e.g., carotid endarterectomies). Traditional skin incisions for carotid endarterectomies are made relative to the midpoint of a line extending from the mastoid process to the suprasternal notch and are typically 10-18 cm in length (Bastounis et al., 2007; Ascher et al., 2005). The same measurement technique is utilized clinically for both male and female patients to identify the position of common carotid artery bifurcation.

Results show that males and females exhibit differential levels common carotid bifurcation with regard to the midpoint between mastoid process and suprasternal notch. As a result, vascular surgeons may be unintentionally making longer than necessary incisions when attempting to surgically locate the level of common carotid bifurcation. New procedures involving smaller incisions (i.e., less than 5 cm) for surgical intervention to the carotid arterial system have been successful both clinically and aesthetically (Ascher et al., 2005). Incorporation of the results of this study regarding differential common carotid bifurcation levels between sexes may aid surgeons in making smaller incisions which would improve scar aesthetics and decrease patient morbidity and mortality.

In support of our predictions, no significant differences were determined between males and females for the level of CB or the CB to the STA, LA, FA, and OA distances. Additionally, no significant differences were determined between the sexes regarding ECA branching pattern. This lack of sex differences in the carotid arterial system may be attributed to the staging of human embryonic vasculature and sexual development.

The formation of embryonic vasculature actually occurs well before embryonic sex differentiation. The embryonic cardiovascular system begins to form early in the third and fourth weeks of human development and the aortic arches give rise to the final embryonic arterial arrangement during the eighth week (Carlson, 2004; Moore & Persaud, 2003). With regard to sexual differentiation of the human embryo, the embryonic reproductive structures are the same for both sexes until approximately the ninth week of development. Male and female fetuses are essentially "unsexed" at the time of vascular formation. Once the final arterial arrangement is established in the embryo, differential growth rates between the sexes later in life would not affect the origin location of the arterial structures. Thus, variation in ECA branching pattern is not expected to occur as a result of sexual differences.

Variation Between Neck Side

Differences in branching pattern between neck sides could be a result of the differential formation of arterial precursors from which the external carotid artery and its branches are derived. Aortic arches 1-2 largely disappear over the course of cardiovascular remodeling, while arches 3-6 persist (Carlson, 2004; Moore & Persaud, 2003). It seems as if the arterial derivatives of arches 3-6 and the ventral aortic root (e.g.,

common carotid arteries, common carotid bifurcation, arch of the aorta, brachiocephalic trunk, pulmonary arteries) exhibit less variation in formation and structure. Variation in ECA branching pattern, as compared with variation in more the centralized structures derived from arches 3-6 / ventral aortic root, could be attributable to the disintegration of the arterial precursors (aortic arches 1 and 2) from which the ECA is derived.

In the fully developed human, the carotid arterial system exhibits differential origin location between the right and left sides of the neck (Figure 12). The common carotid artery can be seen originating from the brachiocephalic trunk on the right, and from the arch of the aorta on the left. Hence, the origin of left carotid arterial system is much lower than the right carotid arterial system. The STA was the only ECA branch that exhibited significant differences in origin location with regard to side. In addition to significant differences in STA origin location between neck sides, the results of this study showed significant difference in the distances from CB to STA between the right and left. The significantly longer distance on the left seems to reflect the higher occurrence of STA origin from the CCA on the left side and may be attributable to the lower primary origin of the CCA (from the arch of the aorta) in comparison with the CCA origin on the right (from the brachiocephalic trunk).

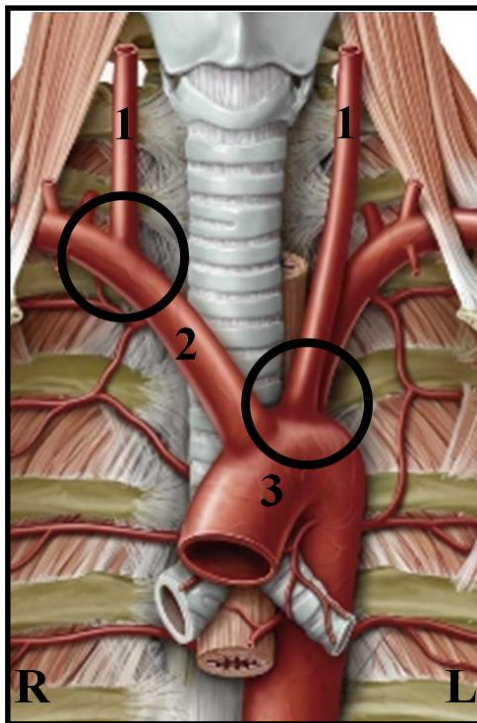


Figure 12. Side differences in the origin of the carotid arterial system. The CCA originates from the brachiocephalic trunk on the right, and from the arch of the aorta on the left. 1 = common carotid artery, 2 = brachiocephalic trunk, 3 = arch of the aorta (Gilroy et al., 2008).

There is controversy surrounding terminology related to the common carotid arterial bifurcation. "Bifurcation" implies that the CCA is dividing into two equal parts (the ICA and ECA); however, the ECA typically exhibits a smaller arterial diameter than the ICA. As a result, some sources consider the ICA to be the continuation of the CCA, and the ECA as a branch of the ICA (Natsis et al., 2011). Furthermore, the CCA, CB and ICA share a mutual developmental origin from the third pair of human embryonic aortic arches, while the ECA and its branches are primarily derived from the first and second pair of aortic arches.

The STA is currently described in the majority of anatomical texts as the first and most caudal branch of the ECA; however, given the results of this and other related studies, the STA origin location may need to be reevaluated to determine if it is actually a branch of the ECA (derived from arches 1-2), or a branch from the CB/CCA (derived

from arch 3). Regardless of development, the multiple STA origin locations and variation frequencies should be incorporated into anatomical texts to adequately reflect the differences in STA origin between neck side to ensure clinicians are provided with accurate information.

Neck length (mastoid process to suprasternal notch) did differ significantly between right and left sides. A significant difference in neck length between sides was not expected to occur due to the lack of major asymmetry in human head and neck positioning. This side difference may be attributable to cadaver head/neck positioning during the process of recording measurements. Specimens were positioned as close to anatomical position as possible prior to performing measurements; however, some specimens were difficult to manipulate due to fixation and inflexible tissue condition. The differential cadaver quality could have affected the measurements.

Clinical Implications

Unfortunately, the results of this study did not allow for the synthesis of a dependable application for clinical use to successfully predict carotid arterial arrangement or to locate the position of specific components of the carotid arterial system using external/bony anatomical landmarks. We did not see the correlation we anticipated between neck lengths (mastoid process to suprasternal notch) or midpoint levels and the level of CB (Figure 13), or the origin locations for the STA, LA, FA, or OA for the sexes or neck side.

The lack of a definitive method for predicting arterial pattern/locations is exceedingly important clinically and emphasizes both the extreme variability in the carotid arterial

system and the increased probability of iatrogenic injury as a result of the high level of unpredictability. These results imply that clinicians may not be able to effectively deduce the exact arterial configuration prior to surgical intervention via the measurement techniques currently utilized (i.e., locating the level of common carotid bifurcation by locating the midpoint between mastoid process and suprasternal notch).

Despite the lack of direct correlation, the results of this study may be used clinically to improve the process of locating the level of CB, and may also facilitate a decrease in incision length during surgical intervention to the carotid arterial system. All carotid bifurcations were observed cranial to the midpoint located centrally between the mastoid process and the suprasternal notch. No significant difference was found for the mean distance of CB from the midpoint with regard to sex or side.

As a result, it is recommended that surgeons continue to locate the midpoint using the same measurement techniques they use currently; however, the incision should be extended cranially only, as opposed to the current standard for making incisions which involves cutting both cranial and caudal to the midpoint. Additionally, initial incisions could be made shorter and only further extended cranially as necessary in male patients due to the lower level of CB with regard to body size. Special attention should be paid when performing surgeries involving the carotid arterial system at/around the level of CB (i.e., carotid endarterectomies and thyroidectomies) in both sexes due to the high variability in STA origin between neck side.

While the bony anatomical landmarks utilized in this study (e.g., mastoid process and suprasternal notch) were chosen due to their current clinical use by vascular surgeons, further studies could incorporate additional bony or palpable anatomical landmarks (i.e.,

gonion, laryngeal cartilages, hyoid bone) in attempt to synthesize a more applicable formula for use in identifying the specific components of the carotid arterial system.

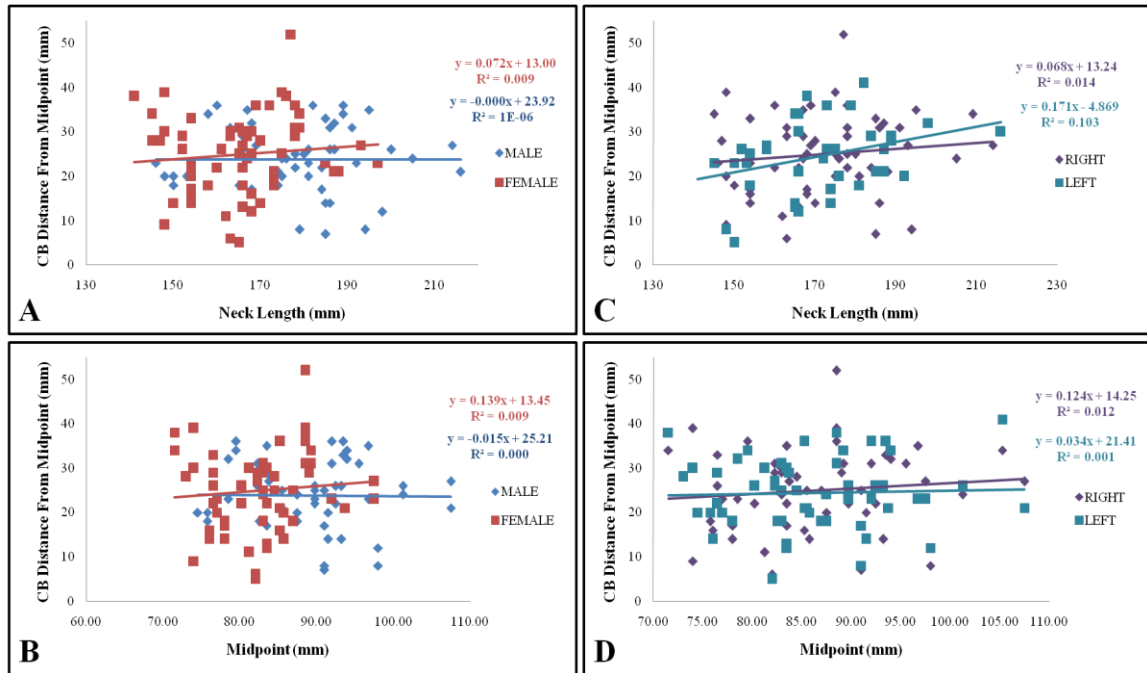


Figure 13. Predicting the location of the common carotid bifurcation using bony anatomical landmarks. No strong correlation was found between neck length (mastoid process to suprasternal notch) or midpoint level and the level of common carotid bifurcation for the sexes (A & B) or neck side (C & D).

Variation Among Ethnic Populations

An ethnic comparison was performed utilizing data from this study population and that from other studies to examine potential ethnic influences on arterial patterning in the carotid arterial system. The origin locations for the STA and the incidence of individual or shared origins for the LA/FA were compared. Previous studies encompassed predominately European and Asian populations while the current study contributed to the paucity of research published on variation of neck vasculature in residents of the United States (Figure 14).

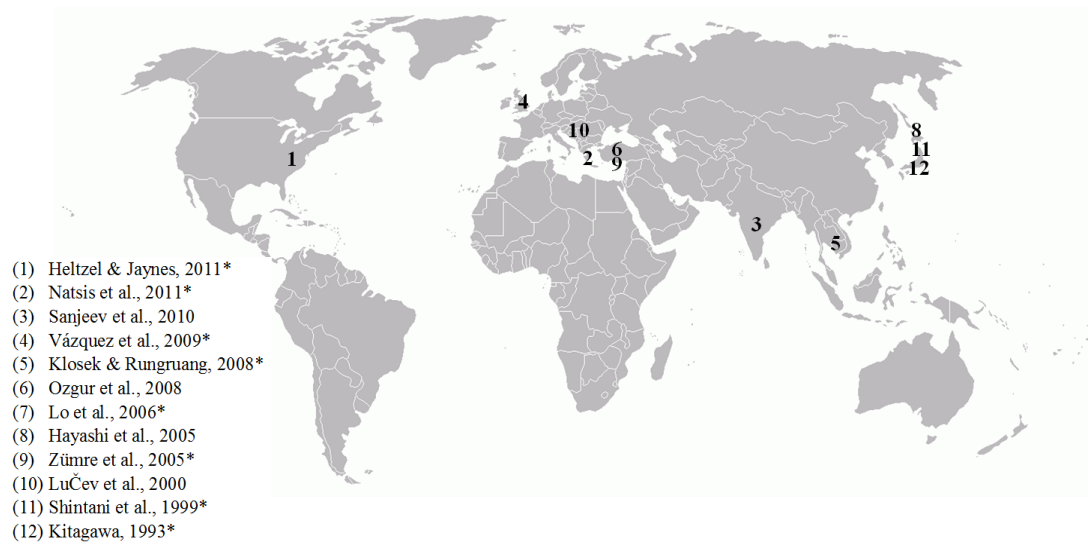


Figure 14. Global study populations. (*) indicates that side differences were noted.

In the majority of ethnic populations it appears that the STA originates most often from the ECA or from the CB and less often from the CCA; however, side differences have been noted. In support of the results from this study population, the STA has also been reported to originate more often from the ECA/CB on the right and from the CCA

on the left in both European and Asian populations (Vázquez et al., 2009; Ozgur et al., 2008; Toni et al., 2004; Kitagawa, 1993).

With regard to the STA origin location, the results of this study were most similar to the results from European populations (specifically Turkey (Ozgur et al., 2008) and Croatia (Lučev et al., 2000)) and showed lesser similarity to Asian populations (specifically Thailand (Klosek & Rungruang, 2008) and Japan (Shintani et al., 1999) (Figure 15A). STA origin location distance from the CB was also compared, and while definitive means were unavailable in the majority of studies, the ranges for the distances were similar across included populations. No specific sexual differences in STA origin location were noted for any of the study populations.

Differences in STA origin location may be attributable to genetic differences between populations. These genetic differences would not directly result from selection pressures, but may instead be derived from random variation generated by mutation. Such mutations within populations could then be propagated by neutral evolutionary processes (e.g., genetic drift). Developmental dynamics such as exposure to teratogens and nutritional deficiencies *in utero* could also result in differential arterial formation and differentiation among populations (Sekhon et al., 2004; Vonnahme et al., 2003).

Similar frequencies of LA and FA origin configurations were noted across ethnic populations. The majority of LA and FA originate individually from the ECA (79%); however, common lingual-facial trunks do occur quite frequently (20%) (Figure 15B). The results of this study were very similar to the results from all ethnic populations included in the comparison.

In summary, no definitive differences could be found between ethnic populations regarding ECA branch patterning of the STA or LA/FA. The differences in ECA branch origin location reported between ethnic populations may also be attributable to ambiguous categorization of vessel origin locations. The STA seems to have the widest range of reported origin location frequencies (e.g., STA originating from the CB/ECA reported in 33% of specimens in some studies as compared to 100% of specimens in others) (Klosek & Rungruang, 2008; Shintani et al., 1999).

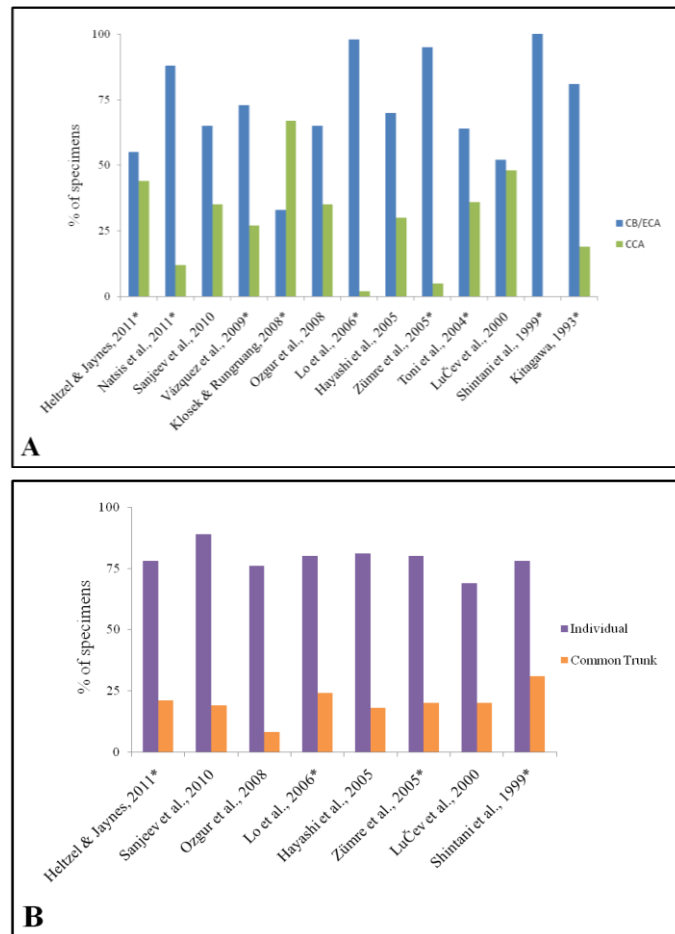


Figure 15. Ethnic comparison: STA and LA/FA origin locations.

(A) STA origin location; the STA originated most often from the CB/ECA in the majority of study populations. (B) LA/FA origin; the LA and FA originated individually in the majority of study populations. (*) indicates that side differences were noted.

Future Approaches

The current study was based on postmortem fixed specimens. While the better approach would be to examine unfixed specimens, fresh tissue is difficult to procure, is very expensive, and is subject to rapid decomposition. Embalming of the specimens is necessary to preserve tissue for extended examination. The common carotid artery is a common site of embalming fluid injection. Therefore manipulation of the carotid system and direct contact with potent chemicals occurring during the embalming process could feasibly reduce tissue size.

While vasculature might exhibit minimal shrinkage when subjected to fixation, it typically remains in position relative to surrounding structures, and any slight reduction in size would be accompanied by a relative size reduction in surrounding bodily tissues. Therefore, due to afore mentioned reasons, the use of fresh specimens should not substantially alter the study results. Further investigation of ECA branching pattern variation could consist of a detailed comparison of fixed and unfixed tissue samples to confirm there is no difference in relative size/location of vessels.

LITERATURE CITED

- Aggarwal, N. R., Krishnamoorthy, T., Devasia, B., Menon, G., & Chandrasekhar, K. (2006). Variant origin of superior thyroid artery, occipital artery and ascending pharyngeal artery from a common trunk from the cervical segment of internal carotid artery. *Surgical and Radiologic Anatomy (English Ed.)*, 28(6), 650-653.
- Anangwe, D., Saidi, H., Ogeng'o, J., & Awori, K. (2008). Anatomical variations of the carotid arteries in adult Kenyans. *East African Medical Journal*, 85(5), 244-247.
- Ascher, E., Hingorani, A., Marks, N., Schutzer, R. W., Mutyala, M., Nahata, S., Yorkovich, W., & Jacob, T. (2005). Mini skin incision for carotid endarterectomy (CEA): A new and safe alternative to the standard approach. *Journal of Vascular Surgery*, 42(6), 1089-1093.
- Ballard, V. L., & Edelberg, J. M. (2005). Harnessing hormonal signaling for cardioprotection. *Science of Aging Knowledge Environment*, 2005(51), re6.
- Bastounis, E., Bakoyiannis, C., Cagiannos, C., Klonaris, C., Filis, C., Bastouni, E. E., & Georgopoulos, S. (2007). A short incision for carotid endarterectomy results in decreased morbidity. *European Journal of Vascular and Endovascular Surgery*, 33(6), 652-656.
- Bell, R., Osborn, T., Dierks, E., Potter, B., & Long, W. (2007). Management of penetrating neck injuries: A new paradigm for civilian trauma. *Journal of Oral and Maxillofacial Surgery*, 65(4), 691-705.
- Biffl, W., Moore, E., Ryu, R., Offner, P., Novak, Z., Coldwell, D., Franciose, R., & Burch, J. (1998). The unrecognized epidemic of blunt carotid arterial injuries: Early diagnosis improves neurologic outcome. *Annals of Surgery*, 228(4), 462-470.

- Buteau-Lozano, H., Ancelin, M., Lardeux, B., Milanini, J., & Perrot-Appanat, M. (2002). Transcriptional regulation of vascular endothelial growth factor by estradiol and tamoxifen in breast cancer cells: A complex interplay between estrogen receptors α and β . *Cancer Research (Baltimore)*, 62(17), 4977-4984
- Carlson, B.M. (2004). *Human embryology and developmental biology* (3rd ed.). Philadelphia: Mosby.
- Chleborad, W. P., & Dawson, D. L. (1990). The profunda femoris artery: Variations and clinical applications. *Clinical Anatomy (New York, N.Y.)*, 3(1), 33-40.
- Ditmars, M. L., Klein, S. R., & Bongard, F. S. (1997). Diagnosis and management of zone III carotid injuries. *Injury*, 28(8), 515-520.
- Drake, R. L., Vogl, W., & Mitchell, A.W. (2005). *Gray's Anatomy for Students* (1st ed.). Philadelphia: Churchill Livingstone.
- Eden, S. V., Meurer, W. J., Sánchez, B. N., Lisabeth, L. D., Smith, M. A., Brown, D. L., & Morgenstern, L. B. (2008). Gender and ethnic differences in subarachnoid hemorrhage. *Neurology*, 71(10), 731-735.
- Ford, C. S., Howard, V. J., & Howard, G. (1986). The sex difference in manifestations of carotid bifurcation disease. *Stroke (1970)*, 17(5), 877-881.
- Fruhstorfer, B. H., Palmer, J., Brydges, S., & Abrahams, P. H. (2010). The use of plastinated prosections for teaching anatomy-the view of medical students on the value of this learning resource. *Clinical Anatomy (New York, N.Y.)*, , n-a-n/a.
- Gilbert, S.F. (2000). *Developmental Biology* (6th ed.). Sunderland (MA): Sinauer Associates.

- Gilroy, A., MacPherson, B., Ross, L., Schuenke, M., Schulte, E., Schumacher, U. (2008). *Atlas of anatomy* (1st softcover ed.). New York: Thieme Medical Publishers.
- Gluncic, V., Petanjek, Z., Marusic, A., & Gluncic, I. (2001). High bifurcation of common carotid artery, anomalous origin of ascending pharyngeal artery and anomalous branching pattern of external carotid artery. *Surgical and Radiologic Anatomy (English Ed.)*, 23(2), 123-125.
- Hartling, R., McGahan, J., Lindfors, K., & Blaisdell, F. (1989). Stab wounds to the neck: Role of angiography. *Radiology*, 172(1), 79-82.
- Hayashi, N., Hori, E., Ohtani, Y., Ohtani, O., Kuwayama, N., & Endo, S. (2005). Surgical anatomy of the cervical carotid artery for carotid endarterectomy. *Neurologia Medico-Chirurgica*, 45(1), 25-9; discussion 30.
- Inamasu, J., & Guiot, B. H. (2005). Iatrogenic carotid artery injury in neurosurgery. *Neurosurgical Review*, 28(4), 239-247.
- International Society for Plastination. (2008). Retrieved November 30, 2010, from <http://isp.plastination.org/index.html>
- Jarvik, J., Philips III, G., Schwab, C., Schwartz, J., & Grossman, R. (1995). Penetrating neck trauma: Sensitivity of clinical examination and cost- effectiveness of angiography. *American Journal of Neuroradiology : AJNR*, 16(4), 647-654.
- Jesmin, S., Mowa, C. N., Sultana, S. N., Shimojo, N., Togashi, H., Iwashima, Y., Kato, N., Sato, A., Sakuma, I., Hiroe, M., Hattori, Y., Yamaguchi, N., & Kobayashi, H. (2010). VEGF signaling is disrupted in the hearts of mice lacking estrogen receptor alpha. *European Journal of Pharmacology*, 641(2-3), 168-178.

- Johnsen, S. H., Joakimsen, O., Singh, K., Stensland, E., Forsdahl, S. H., & Jacobsen, B. K. (2009). Relation of common carotid artery lumen diameter to general arterial dilating diathesis and abdominal aortic aneurysms: The tromsø study. *American Journal of Epidemiology*, 169(3), 330-338.
- Jones, E. A. V., Baron, M. H., Fraser, S. E., & Dickinson, M. E. (2004). Measuring hemodynamic changes during mammalian development. *American Journal of Physiology. Heart and Circulatory Physiology*, 287(4 56-4), H1561-H1569.
- Jones, E.A, le Noble, F., & Eichmann, A. (2006). What determines blood vessel structure? genetic prespecification vs. hemodynamics. *Physiology* (Bethesda, Md.), 21, 388-395.
- Jurkovich, G., Zingarelli, W., Wallace, J., & Curreri, P. (1985). Penetrating neck trauma: Diagnostic studies in the asymptomatic patient. *Journal of Trauma: Injury, Infection, and Critical Care*, 25(9), 819-822.
- Kirkman, T.W. (1996). Statistics to use. Retrieved March 26, 2011, from <http://www.physics.csbsju.edu/stats/>
- Kitagawa, W. (1993). Arterial supply of the thyroid gland in the human fetuses. *Nippon Ika Daigaku Zasshi*, 60(3), 140-155.
- Klosek, S. K., & Rungruang, T. (2008). Topography of carotid bifurcation: Considerations for neck examination. *Surgical and Radiologic Anatomy (English Ed.)*, 30(5), 383-387.
- Koch, S., Nelson, D., Rundek, T., Mandrekar, J., & Rabinstein, A. (2009). Race-ethnic variation in carotid bifurcation geometry. *Journal of Stroke and Cerebrovascular Diseases*, 18(5), 349-353.

- Krejza, J., Arkuszewski, M., Kasner, S. E., Weigele, J., Ustymowicz, A., Hurst, R. W., Cucchiara, B. L., & Messe, S. R. (2006). Carotid artery diameter in men and women and the relation to body and neck size. *Stroke* (1970), 37(4), 1103-1105.
- Levy, D., & Gruber, B. (2010). Neck Trauma. *eMedicine*. Retrieved February 12, 2011 from <http://emedicine.medscape.com/article/827223-overview>
- Liem, K., Bemis, W., Walker, W., & Grande, L. (2000). *Functional anatomy of the vertebrates: an evolutionary perspective* (3rd ed.). Belmont: Brooks Cole.
- Lindekleiv, H. M., Valen-Sendstad, K., Morgan, M. K., Mardal, K., Faulder, K., Magnus, J. H., Waterloo, K., Romner, B., & Ingebrigtsen, T. (2010). Sex differences in intracranial arterial bifurcations. *Gender Medicine*, 7(2), 149-155.
- Lippert, H., Pabst, R. (1985). *Arterial Variations in Man: Classification and Frequency*. Springer.
- Lo, A., Oehley, M., Bartlett, A., Adams, D., Blyth, P., & Al-Ali, S. (2006). Anatomical variations of the common carotid artery bifurcation. *ANZ Journal of Surgery*, 76(11), 970-972.
- Lohan, D., Barkhordarian, F., Saleh, R., Krishnam, M., Salamon, N., Ruehm, S., & Finn, J. (2007). MR angiography at 3 T for assessment of the external carotid artery system. *American Journal of Roentgenology* (1976), 189(5), 1088-1094.
- LuČev, N., Bobinac, D., Marič, I., & Dreščik, I. (2000). Variations of the great arteries in the carotid triangle. *Otolaryngology--Head and Neck Surgery*, 122(4), 590-591.
- Malnar, D., Klasan, G. S., Miletić, D., Bajek, S., Vranić, T. S., Arbanas, J., Bobinac, D., & Čoklo, M. (2010). Properties of the celiac trunk - anatomical study. *Collegium Antropologicum*, 34(3), 917-921.

Mangla, S., & Sclafani, S. J. A. (2008). External carotid arterial injury. *Injury*, 39(11), 1249-1256.

McConnell, D., & Trunkey, D. (1994). Management of penetrating trauma to the neck. *Advances in Surgery (Chicago)*, 27, 97-127.

Menawat, S., Dennis, J., Laneve, L., Frykberg, E., Goldman, M., McCann, R., Hyde, G., & Clagett, G. (1992). Are arteriograms necessary in penetrating zone II neck injuries? *Journal of Vascular Surgery*, 16(3), 397-401.

Meyer, J., Barrett, J., Schuler, J., & Preston Flanigan, D. (1987). Mandatory vs selective exploration for penetrating neck trauma. A prospective assessment. *Archives of Surgery (Chicago.1960)*, 122(5), 592-597.

Monson, D., Saletta, J., & Freeark, R. (1969). Carotid vertebral trauma. *Journal of Trauma: Injury, Infection, and Critical Care*, 9(12), 987-999.

Moore, K., Dalley, A., & Agur, A. (2009). *Clinically oriented anatomy* (6th ed.). Baltimore: Lippincott Williams & Wilkins.

Moore, K., & Persaud, T.V. (2003). *The developing human: clinically oriented embryology* (7th ed.). Philadelphia: Saunders.

Muller, H. R., Brunholzl, C., Radu, E. W., & Buser, M. (1991). Sex and side differences of cerebral arterial caliber. *Neuroradiology*, 33(3), 212-216.

Nakamura, Y., Suzuki, T., & Sasano, H. (2005). Estrogen actions and in situ synthesis in human vascular smooth muscle cells and their correlation with atherosclerosis. *The Journal of Steroid Biochemistry and Molecular Biology*, 93(2-5), 263-268.

- Natsis, K., Raikos, A., Foundos, I., Noussios, G., Lazaridis, N. and Njau, S. N. (2011), Superior thyroid artery origin in Caucasian Greeks: A new classification proposal and review of the literature. *Clinical Anatomy*, 24: n/a. doi: 10.1002/ca.21181
- Netter, F.H. (2002). *Atlas of Human Anatomy* (3rd ed.). Teterboro: Saunders.
- Nicoucar, K., Popova, N., Becker, M., & Dulguerov, P. (2008). Pseudoaneurysm of the external carotid artery after a blunt facial trauma. *Journal of Trauma: Injury, Infection, and Critical Care*, 65(3), E24-27.
- Ogden, C. L., Fryar, C. D., Carroll, M. D., & Flegal, K. M. (2004). Mean body weight, height, and body mass index, united states 1960-2002. *Advance Data from Vital and Health Statistics of the National Center for Health Statistics*, (347), 1-17.
- Ozgur, Z., Govsa, F., & Ozgur, T. (2008). Assessment of origin characteristics of the front branches of the external carotid artery. *The Journal of Craniofacial Surgery*, 19(4), 1159-1166.
- Ramadan, F., Rutledge, R., Oller, D., Howell, P., Baker, C., & Keagy, B. (1995). Carotid artery trauma: A review of contemporary trauma center experiences. *Journal of Vascular Surgery*, 21(1), 46-56.
- Roon, A., & Christensen, N. (1979). Evaluation and treatment of penetrating cervical injuries. *Journal of Trauma: Injury, Infection, and Critical Care*, 19(6), 391-397.
- Sanjeev, I. K., Anita, H., Ashwini, M., Mahesh, U., & Rairam, G. B. (2010). Branching pattern of external carotid artery in human cadavers. *Journal of Clinical and Diagnostic Research*, 4(5), 3128-3133.
- Schulz, U.G., & Rothwell, P. M. (2001). Major variation in carotid bifurcation anatomy: A possible risk factor for plaque development? *Stroke* (1970), 32(11), 2522-2529.

- Schulz, U. G., & Rothwell, P. M. (2001). Sex differences in carotid bifurcation anatomy and the distribution of atherosclerotic plaque. *Stroke* (1970), 32(7), 1525-1531.
- Sekhon, H. S., Proskocil, B. J., Clark, J. A., & Spindel, E. R. (2004). Prenatal nicotine exposure increases connective tissue expression in foetal monkey pulmonary vessels. *The European Respiratory Journal*, 23(6), 906-915.
- Shintani, S., Terakado, N., Alcalde, R. E., Tomizawa, K., Nakayama, S., Ueyama, Y., . . . Matsumura, T. (1999). An anatomical study of the arteries for intraarterial chemotherapy of head and neck cancer. *International Journal of Clinical Oncology*, 4(6), 327-330.
- Toni, R., Della Casa, C., Castorina, S., Malaguti, A., Mosca, S., Roti, E., & Valenti, G. (2004). A meta-analysis of superior thyroid artery variations in different human groups and their clinical implications. *Annals of Anatomy*, 186(3), 255-262.
- Turba, U. C., Uflacker, R., Bozlar, U., & Hagspiel, K. D. (2009). Normal renal arterial anatomy assessed by multidetector CT angiography: Are there differences between men and women? *Clinical Anatomy (New York, N.Y.)*, 22(2), 236-242.
- U.S. Census Bureau. (2000). *Census Summary File – Age Groups and Sex: 2000*. Retrieved December 15, 2010, from <http://factfinder.census.gov>
- Vázquez, T., Cobiella, R., Marañillo, E., Valderrama, F. J., McHanwell, S., Parkin, I., & Sañudo, J. R. (2009). Anatomical variations of the superior thyroid and superior laryngeal arteries. *Head & Neck*, 31(8), 1078-1085.
- von Hagens, G., Tiedemann, K., & Kriz, W. (1987). The current potential of plastination. *Anatomy and Embryology*, 175(4), 411-421.

von Kodolitsch, Y., Ito, W. D., Franzen, O., Lund, G. K., Koschyk, D. H., & Meinertz, T. (2004). Coronary artery anomalies: Part I: Recent insights from molecular embryology. *Zeitschrift Für Kardiologie*, 93(12), 929-937.

Vonnahme, K. A., Hess, B. W., Hansen, T. R., McCormick, R. J., Rule, D. C., Moss, G. E., Murdoch, W.J., Nijlandc, M.J., Skinner, D.C., Nathanielsz, P.W., & Ford, S. P. (2003). Maternal undernutrition from early- to mid-gestation leads to growth retardation, cardiac ventricular hypertrophy, and increased liver weight in the fetal sheep. *Biology of Reproduction*, 69(1), 133-140.

Zümre, Ö., Salbacak, A., Çiçekcibaşı, A., Tuncer, I., & Seker, M. (2005). Investigation of the bifurcation level of the common carotid artery and variations of the branches of the external carotid artery in human fetuses. *Annals of Anatomy*, 187(4), 361-369.